STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 201127

TO: Ralph J Gitomer **Location: REM/3D65/3C18** **Art Unit: 1655** **Wednesday, September 20, 2006** **Case Serial Number: 10/734582**	**From: Paul Schulwitz** **Location: Biotech-Chem Library** **REM-1A65** **Phone: 571-272-2527** **Paul.schulwitz@uspto.gov**

Search Notes

Examiner Gitomer,

Please review the attached search results.
If you have any questions or if you would like to refine the search query, please feel free to contact me at any time.

Thank you for using STIC search services!

Paul Schulwitz
Technical Information Specialist
REM-1A65
571-272-2527

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=> d his nofil

     (FILE 'HOME' ENTERED AT 16:45:56 ON 20 SEP 2006)

     FILE 'HCAPLUS' ENTERED AT 16:46:10 ON 20 SEP 2006
                E US2003-734582/APPS
L1              1 SEA ABB=ON  PLU=ON  US2003-734582/AP
                SEL RN

     FILE 'REGISTRY' ENTERED AT 16:46:45 ON 20 SEP 2006
L2              9 SEA ABB=ON  PLU=ON  (141349-89-5/BI OR 146838-19-9/BI OR
                183869-11-6/BI OR 220127-57-1/BI OR 820350-85-4/BI OR 820350-86
                -5/BI OR 820350-87-6/BI OR 820350-88-7/BI OR 98037-52-6/BI)

     FILE 'HCAPLUS' ENTERED AT 16:46:57 ON 20 SEP 2006
L3              1 SEA ABB=ON  PLU=ON  L1 AND L2
                D IALL HITSTR

     FILE 'REGISTRY' ENTERED AT 16:47:38 ON 20 SEP 2006
                E ABL TYROSINE KINAS/CN
L4              2 SEA ABB=ON  PLU=ON  ("ABL TYROSINE KINASE"/CN OR "ABL TYROSINE
                KINASE-INTERACTING PROTEIN (DROSOPHILA MELANOGASTER)"/CN)
                SEL RN
L5              0 SEA ABB=ON  PLU=ON  (250711-31-0/CRN OR 98037-52-6/CRN)

     FILE 'HCAPLUS' ENTERED AT 16:48:23 ON 20 SEP 2006
L6            475 SEA ABB=ON  PLU=ON  L4
L7            151 SEA ABB=ON  PLU=ON  L4(L)INHIB?
L8            154 SEA ABB=ON  PLU=ON  L4(L)(INHIB? OR BLOCK? OR ANTAG?)
L9              1 SEA ABB=ON  PLU=ON  L8 AND L1
                E ABL TYROSIN/CT

     FILE 'REGISTRY' ENTERED AT 16:49:30 ON 20 SEP 2006
                D L4 1-2

     FILE 'HCAPLUS' ENTERED AT 16:50:32 ON 20 SEP 2006
L10           863 SEA ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)(INHIB? OR
                BLOCK? OR ANTAG?)
                D KWIC
L11           114 SEA ABB=ON  PLU=ON  L8 AND L10
L12           903 SEA ABB=ON  PLU=ON  L8 OR L10
L13           676 SEA ABB=ON  PLU=ON  L12 AND (BAC OR DMA OR PAC OR PKT OR
                THU)/RL
                E ANTIMICROB/CT
                E E7+ALL
L14        107508 SEA ABB=ON  PLU=ON  ANTIMICROBIAL AGENTS+PFT,NT1/CT
L15            16 SEA ABB=ON  PLU=ON  L14 AND L13
                E ANTIBACT/CT
                E E5+ALL
L16         91791 SEA ABB=ON  PLU=ON  ANTIBACTERIAL AGENTS+PFT/CT
                E ANTIVIR/CT
                E E6+ALL
L17         43903 SEA ABB=ON  PLU=ON  ANTIVIRAL AGENTS+PFT/CT
L18            16 SEA ABB=ON  PLU=ON  L12 AND (L14 OR L16 OR L17)
L*** DEL        1 S L18 AND L1
                E SHIGELLA FLEX/CT
                E E4+ALL
L19          8579 SEA ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR SHIGELLA
                E ENTEROPATHOGENIC E. COLI/CT
                E E4+ALL
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                E E2+ALL
L20          3173 SEA ABB=ON  PLU=ON  "ESCHERICHIA COLI (L) ENTEROPATHOGENIC"+PFT
                /CT OR EPEC OR ENTEROPATH?
                E SALMONELLA/CT
                E E3+ALL
L21         44796 SEA ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR SALMONELLA
                E VACCINIA/CT
                E E3+ALL
                E E2+ALL
L22         10572 SEA ABB=ON  PLU=ON  "INFECTION (L) VACCINIA"+PFT/CT OR
                VACCINIA
L23             8 SEA ABB=ON  PLU=ON  L12 AND ((L19 OR L20 OR L21 OR L22))
L24            20 SEA ABB=ON  PLU=ON  L18 OR L15 OR L23

     FILE 'MEDLINE' ENTERED AT 16:59:51 ON 20 SEP 2006
L25             0 SEA ABB=ON  PLU=ON  L4
L26           594 SEA ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)(INHIB? OR
                BLOCK? OR ANTAG?)
                E ANTIMICROB/CT
                E E5+ALL
L27        377531 SEA ABB=ON  PLU=ON  ANTI-INFECTIVE AGENTS+PFT,NT1/CT
                E ANTIBACTER/CT
                E E5+ALL
                E E2+ALL
L28        176983 SEA ABB=ON  PLU=ON  ANTI-BACTERIAL AGENTS+PFT/CT
                E ANTIVIR/CT
                E E5+ALL
L29         55979 SEA ABB=ON  PLU=ON  ANTIVIRAL AGENTS+PFT/CT
                E SHIGELLA FLEX/CT
                E E4+ALL
L30         12500 SEA ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR SHIGELL?
                E ENTEROPATHOGENIC E/CT
                E E. COLI/CT
                E E COLI CT
                E E COLI/CT
                E E3+ALL
                E E2+ALL
L31        246916 SEA ABB=ON  PLU=ON  ESCHERICHIA COLI+PFT,NT/CT OR ECOLI OR E
                COLI OR E. COLI OR ESCHERICHIA? OR ENEROPATHOGEN?
                E SALMONELLA/CT
                E E3+ALL
L32         58416 SEA ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR SALMONELLA
                E VACCINIA/CT
                E E3+ALL
L33         11411 SEA ABB=ON  PLU=ON  VACCINIA+PFT/CT OR VACCINIA
L34            11 SEA ABB=ON  PLU=ON  L26 AND ((L27 OR L28 OR L29 OR L30 OR L31
                OR L32 OR L33))

     FILE 'EMBASE' ENTERED AT 17:06:24 ON 20 SEP 2006
L35           566 SEA ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)(INHIB? OR
                BLOCK? OR ANTAG?)
                E ABL TYROSIN/CT
                E E4+ALL
                E E2+ALL
L36           290 SEA ABB=ON  PLU=ON  ABELSON KINASE+PFT/CT AND (INHIB? OR
                BLOCK? OR ANTAG?)
                E ABL TYR/CT
L37             1 SEA ABB=ON  PLU=ON  ("ABL TYROSINE KINASE INHIBITOR"/CT OR
                "ABL TYROSINE KINASE INHIBITOR: PD, PHARMACOLOGY"/CT)
L38           290 SEA ABB=ON  PLU=ON  L36 OR L37
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L39          767 SEA ABB=ON  PLU=ON  L35 OR L38
                 E ANTIMICROB/CT
                 E E7+ALL
                 E E2+ALL
                 E ANTIINFECTIVE AGENT+PFT/CT
L40      1019250 SEA ABB=ON  PLU=ON  ANTIINFECTIVE AGENT+PFT/CT
                 E ANTIBACTER/CT
                 E E6+ALL
                 E E2+ALL
                 E ANTIVIR/CT
                 E E6+ALL
                 E E2+ALL
L41       276022 SEA ABB=ON  PLU=ON  ANTIVIRUS AGENT+PFT/CT
                 E SHIGELLA FLEX/CT
                 E E5+ALL
L42         8718 SEA ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR SHIGELL?
                 E ENTEROPATHOGENIC E/CT
                 E E6+ALL
L43          112 SEA ABB=ON  PLU=ON  ENTEROPATHOGENIC ESCHERICHIA COLI+PFT/CT
L44         2967 SEA ABB=ON  PLU=ON  L43 OR ENTEROPATHOGEN?
                 E SALMONELLA/CT
                 E E3+ALL
L45        39350 SEA ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR SALMONELLA
                 E VACCINIA/CT
                 E E3+ALL
L46          684 SEA ABB=ON  PLU=ON  VACCINIA+PFT/CT
L47         8912 SEA ABB=ON  PLU=ON  L46 OR VACCINIA
L48          214 SEA ABB=ON  PLU=ON  L39 AND (L40 OR L41 OR L42 OR L43 OR L44
                 OR L45 OR L46 OR L47)
                 D KWIC
L49          212 SEA ABB=ON  PLU=ON  L48 AND INHIB?
                 D KWIC
                 D KWIC 2
                 D KWIC 10
L50          211 SEA ABB=ON  PLU=ON  L39 AND (L40 OR L41)
L51        51883 SEA ABB=ON  PLU=ON  ANTIINFECTIVE AGENT/CT OR ANTIVIRUS
                 AGENT/CT
L52            5 SEA ABB=ON  PLU=ON  L39 AND L51
L53            5 SEA ABB=ON  PLU=ON  L39 AND (L42 OR L43 OR L44 OR L45 OR L46
                 OR L47)
L54            8 SEA ABB=ON  PLU=ON  L52 OR L53

     FILE 'BIOSIS, DRUGU, WPIX' ENTERED AT 17:16:39 ON 20 SEP 2006
L55         1773 SEA ABB=ON  PLU=ON  (ABL OR ABELSON)(3A) KINAS?(5A)(INHIB? OR
                 BLOCK? OR ANTAG?)
L56      2834954 SEA ABB=ON  PLU=ON  BACTERI? OR ANTIBACTER? OR VIR? OR
                 ANTIVIR? OR ANTIMICROB? OR MICROB? OR SHIGELLA OR ENTEROPATHOGE
                 N? OR E. COLI OR ECOLI OR E COLI OR ESCHERICHIA OR SALMONELLA
                 OR VACCINIA
L57          172 SEA ABB=ON  PLU=ON  L55 AND L56
                 D KWIC
                 D KWIC 15
L58           61 SEA ABB=ON  PLU=ON  L57 AND PY<2003

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, WPIX' ENTERED AT 17:31:49 ON 20
     SEP 2006
                 E PENDERGAST A/AU
L59          254 SEA ABB=ON  PLU=ON  ("PENDERGAST A"/AU OR "PENDERGAST A M"/AU
                 OR "PENDERGAST ANN M"/AU OR "PENDERGAST ANN MARIE"/AU OR
                 "PENDERGAST ANNE MARIE"/AU OR "PENDERGAST ANNMARIE"/AU)
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                E BURTON E/AU
L60          262 SEA ABB=ON  PLU=ON  ("BURTON E"/AU OR "BURTON E A"/AU OR
                "BURTON ELIABETH"/AU OR "BURTON ELISABETH A"/AU OR "BURTON
                ELIZABETH"/AU OR "BURTON ELIZABETH A"/AU OR "BURTON ELIZABETH
                ANN"/AU)
L61           17 SEA ABB=ON  PLU=ON  L59 AND L60
L62          499 SEA ABB=ON  PLU=ON  (L59 OR L60)
L63          213 SEA ABB=ON  PLU=ON  L62 AND (ABL OR ABELSON)
L64           20 SEA ABB=ON  PLU=ON  L62 AND (ABL OR ABELSON)(3A) KINAS?(5A)(INH
                IB? OR BLOCK? OR ANTAG?)
L65           35 SEA ABB=ON  PLU=ON  L61 OR L64

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 17:35:21 ON 20 SEP 2006
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FILE COVERS 1907 - 20 Sep 2006  VOL 145 ISS 13
FILE LAST UPDATED: 19 Sep 2006  (20060919/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l3
L1             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2003-734582/AP
L2             9 SEA FILE=REGISTRY ABB=ON  PLU=ON  (141349-89-5/BI OR 146838-19-
                9/BI OR 183869-11-6/BI OR 220127-57-1/BI OR 820350-85-4/BI OR
                820350-86-5/BI OR 820350-87-6/BI OR 820350-88-7/BI OR 98037-52-
                6/BI)
L3             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
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INSTANT APPLICATION

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=> d l3 iall hitstr

L3   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:16965  HCAPLUS  Full-text
DOCUMENT NUMBER:          142:107361
ENTRY DATE:               Entered STN:  09 Jan 2005
TITLE:                    Method of blocking pathogen infection
INVENTOR(S):              Pendergast, Ann Marie; Burton, Elizabeth A.
PATENT ASSIGNEE(S):       Duke University, USA
SOURCE:                   U.S. Pat. Appl. Publ., 20 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
```

INT. PATENT CLASSIF.:
MAIN: C12Q001-68
SECONDARY: C12Q001-48
US PATENT CLASSIF.: 435006000; 435015000
CLASSIFICATION: 1-5 (Pharmacology)
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005003377	A1	20050106	US 2003-734582		20031215 <--
PRIORITY APPLN. INFO.:			US 2002-432989P	P	20021213
			US 2003-507088P	P	20031001

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2005003377 •	ICM	C12Q001-68
	ICS	C12Q001-48
	INCL	435006000; 435015000
	IPCI	C12Q0001-68 [ICM,7]; C12Q0001-48 [ICS,7]
	IPCR	C12Q0001-18 [I,A]; C12Q0001-18 [I,C*]; C12Q0001-48 [I,A]; C12Q0001-48 [I,C*]; C12Q0001-68 [I,A]; C12Q0001-68 [I,C*]
	NCL	435/006.000; 435/015.000
	ECLA	C12Q001/18; C12Q001/48B; C12Q001/68M10B

ABSTRACT:
The present invention relates, in general, to pathogens and, in particular, to a method of blocking pathogen infection and to a method of identifying agents suitable for use in such a method.

SUPPL. TERM: antibacterial antimicrobial Abl Arg kinase Shigella infection
INDEX TERM: G proteins (guanine nucleotide-binding proteins)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(CDC42; method of blocking pathogen infection)
INDEX TERM: Rho protein (G protein)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(Crk substrate; method of blocking pathogen infection)
INDEX TERM: Proteins
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(GST-Crk; method of blocking pathogen infection)
INDEX TERM: G proteins (guanine nucleotide-binding proteins)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(Rac; method of blocking pathogen infection)
INDEX TERM: Antibacterial agents
Antimicrobial agents
Antiviral agents
Drug screening
Escherichia coli
Pathogen
Salmonella
Shigella flexneri
Signal transduction, biological
Vaccinia virus
(method of blocking pathogen infection)
INDEX TERM: 98037-52-6, Abl kinase 141349-89-5, Src

kinase **146838-19-9**, Arg kinase **183869-11-6**
, Protein kinase Crk
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(method of blocking pathogen infection)

INDEX TERM: **220127-57-1**, STI571
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of blocking pathogen infection)

INDEX TERM: **820350-85-4 820350-86-5**
820350-87-6 820350-88-7
ROLE: PRP (Properties)
(unclaimed nucleotide sequence; method of blocking pathogen infection)

IT **98037-52-6**, Abl kinase **141349-89-5**, Src kinase
146838-19-9, Arg kinase **183869-11-6**, Protein kinase Crk
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method of blocking pathogen infection)
RN 98037-52-6 HCAPLUS
CN Kinase (phosphorylating), gene abl protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141349-89-5 HCAPLUS
CN Kinase (phosphorylating), gene src protein (9CI) (CA INDEX NAME)

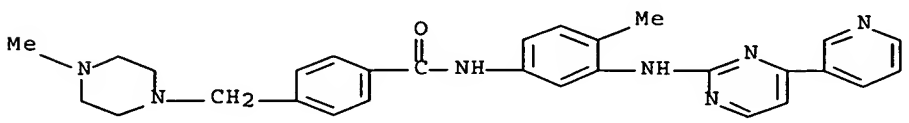
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146838-19-9 HCAPLUS
CN Kinase (phosphorylating), gene arg protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 183869-11-6 HCAPLUS
CN Kinase (phosphorylating), protein, CRK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **220127-57-1**, STI571
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of blocking pathogen infection)
RN 220127-57-1 HCAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

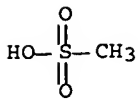
CM 1

CRN 152459-95-5
CMF C29 H31 N7 O



CM 2

CRN 75-75-2
CMF C H4 O3 S



IT 820350-85-4 820350-86-5 820350-87-6
820350-88-7
RL: PRP (Properties)
(unclaimed nucleotide sequence; method of blocking pathogen infection)
RN 820350-85-4 HCAPLUS
CN DNA, d(A-G-A-A-G-C-T-T-T-G-C-A-A-C-A-A-A-C-T-A-C-T-G-C-T-T-G-A) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 820350-86-5 HCAPLUS
CN DNA, d(G-C-G-C-T-C-T-A-G-A-G-G-A-A-G-A-G-C-C-A-T-A-T-A-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 820350-87-6 HCAPLUS
CN DNA, d(A-T-G-T-T-C-G-A-A-C-A-A-C-G-C-G-T-A-A-A-T-T-C-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 820350-88-7 HCAPLUS
CN DNA, d(A-T-G-C-C-G-T-A-T-T-T-T-T-T-C-A-A-T-T-T-T-T-T-A-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PRIOR ART SEARCH

```
=> d que l24
L4            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("ABL TYROSINE KINASE"/CN OR
                "ABL TYROSINE KINASE-INTERACTING PROTEIN (DROSOPHILA MELANOGAST
                ER)"/CN)
L8          154 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4(L)(INHIB? OR BLOCK? OR
                ANTAG?)
L10         863 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)
                (INHIB? OR BLOCK? OR ANTAG?)
L12         903 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 OR L10
L13         676 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND (BAC OR DMA OR PAC OR
                PKT OR THU)/RL
L14      107508 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIMICROBIAL AGENTS+PFT,NT1/C
                T
L15          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND L13
L16       91791 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIBACTERIAL AGENTS+PFT/CT
L17       43903 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIVIRAL AGENTS+PFT/CT
L18          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND (L14 OR L16 OR L17)
L19        8579 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR
                SHIGELLA
L20        3173 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ESCHERICHIA COLI (L)
                ENTEROPATHOGENIC"+PFT/CT OR EPEC OR ENTEROPATH?
L21       44796 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR
                SALMONELLA
L22       10572 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "INFECTION (L) VACCINIA"+PFT/C
                T OR VACCINIA
L23           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND ((L19 OR L20 OR L21
                OR L22))
L24          20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18 OR L15 OR L23


=> fil medline
FILE 'MEDLINE' ENTERED AT 17:35:48 ON 20 SEP 2006

 FILE LAST UPDATED: 19 Sep 2006 (20060919/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l34
L26         594 SEA FILE=MEDLINE ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)
                (INHIB? OR BLOCK? OR ANTAG?)
L27      377531 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTI-INFECTIVE AGENTS+PFT,NT1/
```

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                CT
L28        176983 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTI-BACTERIAL AGENTS+PFT/CT
L29         55979 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIVIRAL AGENTS+PFT/CT
L30         12500 SEA FILE=MEDLINE ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR
                  SHIGELL?
L31        246916 SEA FILE=MEDLINE ABB=ON  PLU=ON  ESCHERICHIA COLI+PFT,NT/CT OR
                  ECOLI OR E COLI OR E. COLI OR ESCHERICHIA? OR ENEROPATHOGEN?
L32         58416 SEA FILE=MEDLINE ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR
                  SALMONELLA
L33         11411 SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINIA+PFT/CT OR VACCINIA
L34            11 SEA FILE=MEDLINE ABB=ON  PLU=ON  L26 AND ((L27 OR L28 OR L29
                  OR L30 OR L31 OR L32 OR L33))


=> fil embase
FILE 'EMBASE' ENTERED AT 17:35:57 ON 20 SEP 2006
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 FILE COVERS 1974 TO 20 Sep 2006 (20060920/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 EMBASE is now updated daily.  SDI frequency remains weekly (default)
 and biweekly.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l54
L35           566 SEA FILE=EMBASE ABB=ON  PLU=ON  (ABL OR ABELSON)(3A)KINAS?(5A)(
                  INHIB? OR BLOCK? OR ANTAG?)
L36           290 SEA FILE=EMBASE ABB=ON  PLU=ON  ABELSON KINASE+PFT/CT AND
                  (INHIB? OR BLOCK? OR ANTAG?)
L37             1 SEA FILE=EMBASE ABB=ON  PLU=ON  ("ABL TYROSINE KINASE INHIBITOR
                  "/CT OR "ABL TYROSINE KINASE INHIBITOR: PD, PHARMACOLOGY"/CT)
L38           290 SEA FILE=EMBASE ABB=ON  PLU=ON  L36 OR L37
L39           767 SEA FILE=EMBASE ABB=ON  PLU=ON  L35 OR L38
L42          8718 SEA FILE=EMBASE ABB=ON  PLU=ON  SHIGELLA FLEXNERI+PFT/CT OR
                  SHIGELL?
L43           112 SEA FILE=EMBASE ABB=ON  PLU=ON  ENTEROPATHOGENIC ESCHERICHIA
                  COLI+PFT/CT
L44          2967 SEA FILE=EMBASE ABB=ON  PLU=ON  L43 OR ENTEROPATHOGEN?
L45         39350 SEA FILE=EMBASE ABB=ON  PLU=ON  SALMONELLA+PFT,NT/CT OR
                  SALMONELLA
L46           684 SEA FILE=EMBASE ABB=ON  PLU=ON  VACCINIA+PFT/CT
L47          8912 SEA FILE=EMBASE ABB=ON  PLU=ON  L46 OR VACCINIA
L51         51883 SEA FILE=EMBASE ABB=ON  PLU=ON  ANTIINFECTIVE AGENT/CT OR
                  ANTIVIRUS AGENT/CT
L52             5 SEA FILE=EMBASE ABB=ON  PLU=ON  L39 AND L51
L53             5 SEA FILE=EMBASE ABB=ON  PLU=ON  L39 AND (L42 OR L43 OR L44 OR
                  L45 OR L46 OR L47)
L54             8 SEA FILE=EMBASE ABB=ON  PLU=ON  L52 OR L53


=> fil biosis drugu wpix
FILE 'BIOSIS' ENTERED AT 17:36:38 ON 20 SEP 2006
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=> d que l58
L55         1773 SEA (ABL OR ABELSON)(3A) KINAS?(5A)(INHIB? OR BLOCK? OR
                 ANTAG?)
L56      2834954 SEA BACTERI? OR ANTIBACTER? OR VIR? OR ANTIVIR? OR ANTIMICROB?
                 OR MICROB? OR SHIGELLA OR ENTEROPATHOGEN? OR E. COLI OR ECOLI
                 OR E COLI OR ESCHERICHIA OR SALMONELLA OR VACCINIA
L57          172 SEA L55 AND L56
L58           61 SEA L57 AND PY<2003


=> dup rem l24 l34 l54 l58
FILE 'HCAPLUS' ENTERED AT 17:37:00 ON 20 SEP 2006
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PROCESSING COMPLETED FOR L24
PROCESSING COMPLETED FOR L34
PROCESSING COMPLETED FOR L54
PROCESSING COMPLETED FOR L58
L66           88 DUP REM L24 L34 L54 L58 (12 DUPLICATES REMOVED)
                 ANSWERS '1-20' FROM FILE HCAPLUS
                 ANSWERS '21-28' FROM FILE MEDLINE
                 ANSWERS '29-32' FROM FILE EMBASE
                 ANSWERS '33-64' FROM FILE BIOSIS
                 ANSWERS '65-87' FROM FILE DRUGU
                 ANSWER '88' FROM FILE WPIX

=> d l66 ibib ab hitind 1-64;d ibib ab 65-88

L66  ANSWER 1 OF 88  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:622070  HCAPLUS  Full-text
DOCUMENT NUMBER:          143:166065
TITLE:                    Disabling poxvirus pathogenesis by inhibition
                          of Abl-family tyrosine kinases
AUTHOR(S):                Reeves, Patrick M.; Bommarius, Bettina; Lebeis, Sarah;
                          McNulty, Shannon; Christensen, Jens; Swimm, Alyson;
                          Chahroudi, Ann; Chavan, Rahul; Feinberg, Mark B.;
                          Veach, Darren; Bornmann, William; Sherman, Melanie;
                          Kalman, Daniel
CORPORATE SOURCE:         Microbiology and Molecular Genetics Graduate Program,
                          Emory University School of Medicine, Atlanta, 30322,
                          Georgia
```

SOURCE: Nature Medicine (New York, NY, United States) (2005), 11(7), 731-739
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Poxviridae family members **vaccinia** and variola virus enter mammalian cells, replicate outside the nucleus and produce virions that travel to the cell surface along microtubules, fuse with the plasma membrane and egress from infected cells toward apposing cells on actin-filled membranous protrusions. The authors show that cell-associated enveloped virions (CEV) use Abl- and Src- family tyrosine kinases for actin motility, and that these kinases act in a redundant fashion, perhaps permitting motility in a greater range of cell types. Addnl., release of CEV from the cell requires Abl- but not Src-family tyrosine kinases, and is **blocked** by STI-571 (Gleevec), an **Abl**-family **kinase inhibitor** used to treat chronic myelogenous leukemia in humans. Finally, the authors show that STI-571 reduces viral dissemination by five orders of magnitude and promotes survival in infected mice, suggesting possible use for this drug in treating smallpox or complications associated with vaccination. This therapeutic approach may prove generally efficacious in treating microbial infections that rely on host tyrosine kinases, and, because the drug targets host but not viral mols., this strategy is much less likely to engender resistance compared to conventional antimicrobial therapies.

CC 1-5 (Pharmacology)

ST Gleevec antiviral poxvirus **Abl** tyrosine **kinase inhibitor**

IT **Antiviral agents**
Human
Poxviridae
Vaccinia virus
(disabling poxvirus pathogenesis by **inhibition** of **Abl** -family tyrosine **kinases**)

IT **Infection**
(**vaccinia**; disabling poxvirus pathogenesis by **inhibition** of **Abl**-family tyrosine **kinases**)

IT Infection
(variola; disabling poxvirus pathogenesis by **inhibition** of **Abl**-family tyrosine **kinases**)

IT 220127-57-1, Gleevec
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(disabling poxvirus pathogenesis by **inhibition** of **Abl** -family tyrosine **kinases**)

IT **98037-52-6**, **Abl** tyrosine **kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; disabling poxvirus pathogenesis by **inhibition** of **Abl**-family tyrosine **kinases**)

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 2 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:665357 HCAPLUS Full-text
DOCUMENT NUMBER: 141:346235
TITLE: **Enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals
AUTHOR(S): Swimm, Alyson; Bommarius, Bettina; Li, Yue; Cheng, David; Reeves, Patrick; Sherman, Melanie; Veach, Darren; Bornmann, William; Kalman, Daniel
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, 30322, USA

SOURCE. Molecular Biology of the Cell (2004), 15(8), 3520-3529
CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER: American Society for Cell Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Enteropathogenic** Escherichia coli (**EPEC**) are deadly contaminants in water and food and induce protrusion of actin-rich membrane pedestals beneath themselves upon attachment to intestinal epithelia. **EPEC** then causes intestinal inflammation, diarrhea, and, among children, death. Here, we show that **EPEC** uses multiple tyrosine kinases for formation of pedestals, each of which is sufficient but not necessary. Tir. In particular, we show that Abl and Arg, members of the Abl family of tyrosine kinases, localize and are activated in pedestals. We also show that pyrido[2,3-d]pyrimidine (PD) compds., which **inhibit Abl**, Arg, and related **kinases**, **block** pedestal formation. Finally, we show that Abl and Arg are sufficient for pedestal formation in the absence of other tyrosine kinase activity, but they are not necessary. Our results suggest that addnl. kinases that are sensitive to inhibition by PD also can suffice. Together, these results suggest that **EPEC** has evolved a mechanism to use any of several functionally redundant tyrosine kinases during pathogenesis, perhaps facilitating its capacity to infect different cell types. Moreover, PD compds. are being developed to treat cancers caused by dysregulated Abl. Our results raise the possibility that PD may be useful in treating **EPEC** infections, and because PD affects host and not bacterium, selecting resistant strains may be far less likely than with conventional antibiotics.

CC 10-1 (Microbial, Algal, and Fungal Biochemistry)

ST **enteropathogenic** Escherichia tyrosine kinase redundancy actin pedestal formation

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Tir (translocated intimin receptor); **enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT Organelle
(actin pedestal; **enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT Virulence (microbial)
(**enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT **Escherichia coli**
(**enteropathogenic**; **enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT Phosphorylation, biological
(protein; **enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT **Antibacterial agents**
(sensitivity of actin pedestal-forming tyrosine kinases of **enteropathogenic** Escherichia coli to pyridopyrimidine compds. in relation to)

IT 60-18-4, L Tyrosine, biological studies 98037-52-6, Protein tyrosine kinase Abl 146838-19-9, Arg kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT 80449-02-1, Protein tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pyridopyrimidine compound-sensitive; **enteropathogenic** Escherichia coli use redundant tyrosine kinases to form actin pedestals)

IT 254-61-5D, Pyrido[2,3-d]pyrimidine, derivs.

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor; enteropathogenic Escherichia coli use redundant tyrosine kinases to form actin pedestals)
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 3 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2002:950285 HCAPLUS Full-text
DOCUMENT NUMBER: 139:17213
TITLE: **Inhibition** of Bcr-**Abl** **kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells
AUTHOR(S): Huang, Mei; Dorsey, Jay F.; Epling-Burnette, P. K.; Nimmanapalli, Ramadevi; Landowski, Terry H.; Mora, Linda B.; Niu, Guilian; Sinibaldi, Dominic; Bai, Fanqi; Kraker, Alan; Yu, Hua; Moscinski, Lynn; Wei, Sheng; Djeu, Julie; Dalton, William S.; Bhalla, Kapil; Loughran, Thomas P.; Wu, Jie; Jove, Richard
CORPORATE SOURCE: Molecular Oncology, H Lee Moffitt Cancer Center, Research Institute, Tampa, FL, 33612, USA
SOURCE: Oncogene (2002), 21(57), 8804-8816
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chronic myelogenous leukemia (CML) is a myeloproliferative disease characterized by the BCR-ABL genetic translocation and constitutive activation of the Abl tyrosine kinase. Among members of the Signal Transducers and Activators of Transcription (STAT) family of transcription factors, Stat5 is activated by the Bcr-Abl kinase and is implicated in the pathogenesis of CML. We recently identified PD180970 as a new and highly potent **inhibitor** of Bcr-**Abl** **kinase**. In this study, we show that **blocking** Bcr-**Abl** **kinase** activity using PD180970 in the human K562 CML cell line resulted in inhibition of Stat5 DNA-binding activity with an IC50 of 5 nM. Furthermore, abrogation of Abl kinase-mediated Stat5 activation suppressed cell proliferation and induced apoptosis in K562 cells, but not in the Bcr-Abl-neg. myeloid cell lines, HEL 92.1.7 and HL-60. Dominant-neg. Stat5 protein expressed from a **vaccinia** virus vector also induced apoptosis of K562 cells, consistent with earlier studies that demonstrated an essential role of Stat5 signaling in growth and survival of CML cells. RNA and protein analyses revealed several candidate target genes of Stat5, including Bcl-x, Mcl-1, c-Myc and cyclin D2, which were down-regulated after treatment with PD180970. In addition, PD180970 inhibited Stat5 DNA-binding activity in cultured primary leukemic cells derived from CML patients. To detect activated Stat5 in CML patient specimens, we developed an immunocytochem. assay that can be used as a mol. end-point assay to monitor inhibition of Bcr-Abl signaling. Moreover, PD180970 blocked Stat5 signaling and induced apoptosis of STI-571 (Gleevec, Imatinib)-resistant Bcr-Abl-pos. cells. Together, these results suggest that the mechanism of action of PD180970 involves inhibition of Bcr-Abl-mediated Stat5 signaling and provide further evidence that compds. in this structural class may represent potential therapeutic agents for CML.

CC 1-6 (Pharmacology)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-x; **inhibition** of Bcr-**Abl** **kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D2; **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Mcl-1 (myeloid cell leukemia sequence-1); **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT5 (signal transducer and activator of transcription 5); **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Drug resistance
(antitumor; **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-myc; **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for cyclin D2, expression of; **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Antitumor agents
Apoptosis
Cell cycle
Chronic myeloid leukemia
Human
Signal transduction, biological
(**inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT Antitumor agents
(resistance to; **inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT 138238-67-2, Bcr-Abl kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT 287204-45-9, PD180970
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
IT 220127-57-1, STI-571
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibition** of Bcr-**Abl kinase** activity by PD180970 **blocks** constitutive activation of Stat5 and growth of CML cells)
REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 4 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:149165 HCAPLUS Full-text
DOCUMENT NUMBER: 144:226245
TITLE: N-Phenyl-2-pyrimidinamine derivatives for the treatment of immunodeficiency disease-causing viral infections
INVENTOR(S): Zeichner, Steven; Krishnan, Vyjayanthi
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006017353	A2	20060216	WO 2005-US24922	20050713
WO 2006017353	A3	20060330		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-588015P P 20040713
OTHER SOURCE(S): MARPAT 144:226245

AB The invention discloses treatment of cells or humans carrying or infected with a virus capable of causing an immunodeficiency disease with particular compds., including N-phenyl-2-pyrimidinamine derivs. (Markush included), as well as medicaments comprising those compds. and uses thereof. Compds. of the invention include imatinib mesylate.

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

IT AIDS (disease)
Anti-AIDS agents
Antiviral agents
Combination chemotherapy
Drug interactions
Gene expression profiles, animal
Human
Human immunodeficiency virus
Human immunodeficiency virus 1
Lymphocyte
Monocyte
Prophylaxis
(N-phenyl-2-pyrimidinamine derivs. for treatment of immunodeficiency disease-causing viral infections)

IT **Antiviral agents**
(resistance to; N-phenyl-2-pyrimidinamine derivs. for treatment of immunodeficiency disease-causing viral infections)

IT 127779-20-8, Saquinavir

RL: BSU (Biological study, unclassified), PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-phenyl-2-pyrimidinamine derivs. for treatment of immunodeficiency disease-causing viral infections)

IT 30516-87-1, AZT 152459-95-5, Imatinib 220127-57-1, Imatinib mesylate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-phenyl-2-pyrimidinamine derivs. for treatment of immunodeficiency disease-causing viral infections)

IT 98037-52-6, Abl kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; N-phenyl-2-pyrimidinamine derivs. for treatment of immunodeficiency disease-causing viral infections)

L66 ANSWER 5 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:13464 HCAPLUS Full-text
DOCUMENT NUMBER: 144:101073
TITLE: therapeutic uses of kinase inhibitors, and compositions thereof
INVENTOR(S): Caligiuri, Maureen G.; Kley, Nikolai A.; Murthi, Krishna K.
PATENT ASSIGNEE(S): GPC Biotech, Inc., USA
SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006002119	A2	20060105	WO 2005-US21843	20050617

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-580868P P 20040618
OTHER SOURCE(S): MARPAT 144:101073

AB The invention pertains to inhibitors of various kinases (e.g. S/T kinases, Tyr kinases, etc.), which inhibitors are previously known as cyclin dependent kinase inhibitors (CDKs). The inhibitors of the invention are capable of inhibiting various wild-type and mutant form kinases, including drug-resistant forms of mutant kinases. Thus, the kinase inhibitors are useful in treating a wide range of diseases/conditions associated with abnormal functions/excessive activities of the target kinases, including mutant kinases. The invention further provides methods for treating cancers, tumors and patients which are resistant or refractory to other therapeutic agents. Pharmaceutical compns. and packaged pharmaceuticals with instructions of these inhibitors, and methods of using these inhibitors are also provided.

IC ICM A61K031-416
ICS A61P035-00; A61P035-02; A61P043-00; A61P025-28; A61P025-16;

A61P009-10; A61P035 04

CC 1-12 (Pharmacology)
Section cross-reference(s): 25, 63

IT Chimeric gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BCR-ABL, disease related to; kinase inhibitors for therapeutic use)

IT Macrolides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epothilones; kinase inhibitors for therapeutic use)

IT AIDS (disease)
Acute lymphocytic leukemia
Acute myeloid leukemia
Acute promyelocytic leukemia
Adenoma
Adhesion, biological
Allergy
Allergy inhibitors
Alopecia
Alzheimer's disease
Analgesics
Anaphylaxis
Anemia (disease)
Angiogenesis
Angiogenesis inhibitors
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Anti-ischemic agents
Antiarthritics
Antiasthmatics
Antibacterial agents
Antibiotics
Anticholesteremic agents
Anticonvulsants
Antidepressants
Antidiabetic agents
Antidiarrheals
Antiemetics
Antihypertensives
Antiobesity agents
Antiparkinsonian agents
Antipsychotics
Antirheumatic agents
Antitumor agents
Antiviral agents
Apoptosis
Arthritis
Asthma
Atherosclerosis
Autoimmune disease
B-cell leukemia
Bladder, neoplasm
Blood, disease
Blood vessel, disease
Bone, disease
Bone, neoplasm
Bone marrow, disease

Brain, disease
Brain, neoplasm
Bronchi, neoplasm
Cachexia
Calculi, biliary
Carcinoma
Cardiovascular agents
Cartilage, disease
Cell cycle
Cell differentiation
Cell migration
Cell morphology
Cell proliferation
Chronic myeloid leukemia
Cirrhosis
Cognition enhancers
Cognitive disorders
Combination chemotherapy
Contraceptives
Cytotoxic agents
Dermatitis
Dermatomyositis
Diabetes mellitus
Diarrhea
Digestive tract, neoplasm
Down's syndrome
Drug delivery systems
Drug resistance
Eating disorders
Epilepsy
Esophagus, disease
Esophagus, neoplasm
Fibrosis
Filovirus
Gastrointestinal agents
Glaucoma (disease)
Gout
Graves' disease
Head and Neck, disease
Head and Neck, neoplasm
Hematopoiesis
Hepatitis
Hodgkin's disease
Human
Human immunodeficiency virus
Hypercholesterolemia
Hypertension
Hypoxia
Immune disease
Immunomodulators
Immunosuppressants
Infection
Inflammation
Ischemia
Kidney, disease
Kidney, neoplasm
Leukemia
Leukocytopenia
Liver, disease
Liver, neoplasm

Lung, disease
Lung, neoplasm
Lyme disease
Lymph node, disease
Lymphoma
Mammary gland, disease
Mammary gland, neoplasm
Mastocytoma
Melanoma
Meningitis
Metabolic disorders
Microtubule
Multidrug resistance
Multiple myeloma
Multiple sclerosis
Muscle, disease
Mutation
Myasthenia gravis
Myelodysplastic syndromes
Neoplasm
Nervous system, disease
Nervous system agents
Neurofibrillary tangle
Neurotoxicity
Niemann-Pick disease
Obesity
Osteoarthritis
Osteoporosis
Ovary, disease
Ovary, neoplasm
Pain
Pancreas, disease
Pancreas, neoplasm
Parasiticides
Parkinson's disease
Peritoneum, neoplasm
Prion diseases
Prostate gland, disease
Prostate gland, neoplasm
Psoriasis
Psychotropics
Rheumatoid arthritis
Sarcoma
Schizophrenia
Sjogren syndrome
Skin, disease
Skin, neoplasm
Spleen, disease
Stomach, disease
Stomach, neoplasm
T-cell leukemia
Testis, disease
Testis, neoplasm
Thyroid gland, neoplasm
Transplant rejection
Urticaria
Vitiligo
Vomiting
Dyslipidemia
RL: BIOL (Biological study)

(kinase inhibitors for therapeutic use)

IT Anthracyclines
Taxanes
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(kinase inhibitors for therapeutic use)

IT Peptides, biological studies
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(toxic; kinase inhibitors for therapeutic use)

IT Alkaloids, biological studies
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vinca; kinase inhibitors for therapeutic use)

IT 138238-67-2, Bcr-abl kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(and mutations, T315I; kinase **inhibitors** for therapeutic use)

IT 50-18-0, Cytoxan
RL: **PAC (Pharmacological activity)**; BIOL (Biological study)
(kinase inhibitors for therapeutic use)

IT 784210-86-2P 784211-90-1P
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(kinase inhibitors for therapeutic use)

IT 50-76-0, Actinomycin D 53-79-2, Puromycin 57-22-7, Vincristine 64-86-8, Colchicine 64-86-8D, Colchicine, derivs. 641-28-1, Allocolchicine 865-21-4, Vinblastine 1239-45-8, Ethidium bromide 1393-88-0, Gramicidin D 2001-95-8, Valinomycin 2730-71-4, Thiocolchicine 2998-57-4, Estramustine 4375-07-9, Epipodophyllotoxin 7689-03-4, Camptothecin 31430-18-9, Nocodazole 33069-62-4, Paclitaxel 33069-62-4D, Taxol, derivs. 33419-42-0, Etoposide 35846-53-8, Maytansine 42318-55-8D, 1H-Pyrazolo[1,5-a]indole, derivs. 53643-48-4, Vindesine 71486-22-1, Vinorelbine 90996-54-6, Rhizoxin 91421-42-0, Rubitecan 91421-43-1, 9-Aminocamptothecin 97614-65-8, Lamellarin D 97682-44-5 100286-90-6, CPT-11 103614-76-2, Halichondrin B 110417-88-4, Dolastatin 10 123948-87-8, Hycamptin 127943-53-7, Discodermolide 149882-10-0, Lurtotecan 151069-12-4, NB-506 152044-53-6, Epothilone A 152044-54-7, Epothilone B 155773-58-3, GI 147211C 169869-90-3, DX-8951f 171335-80-1, Exatecan 174402-32-5, J107088 215604-74-3, BAY 38-3441 516494-06-7 516494-08-9 516494-11-4 516494-13-6 516494-14-7 516494-16-9 516494-18-1 516494-20-5 516494-22-7 516494-24-9 516494-26-1 784211-18-3 784211-19-4 784211-20-7 784211-21-8 784211-22-9 784211-23-0 784211-24-1 784211-25-2 784211-26-3 784211-27-4 784211-28-5 784211-29-6 784211-30-9 784211-31-0 784211-32-1 784211-33-2 784211-34-3 784211-35-4 784211-36-5 784211-37-6 784211-39-8 784211-40-1 784211-41-2 784211-42-3 784211-44-5 784211-45-6 784211-46-7 784211-47-8 784211-49-0 784211-50-3 784211-51-4 784211-52-5 784211-53-6 784211-54-7 784211-55-8 784211-56-9 784211-57-0 784211-58-1 784211-59-2 784211-60-5 784211-66-1 784211-68-3 784211-69-4 784211-70-7 784211-71-8 784211-72-9 784211-73-0 784211-74-1 784211-75-2 784211-76-3 784211-77-4 784211-78-5 784211-79-6 784211-80-9 784211-81-0 784211-82-1 784211-83-2 784211-84-3 784211-85-4 784211-86-5 784211-87-6 784211-88-7 784211-89-8 784211-91-2 784211-92-3 784211-93-4 784211-94-5 784211-95-6 784211-97-8 808742-08-7 808742-13-4 808742-83-8
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(kinase inhibitors for therapeutic use)

L66 ANSWER 6 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1289100 HCAPLUS Full-text
DOCUMENT NUMBER: 144:36367
TITLE: Preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase inhibitors with improved solubility properties
INVENTOR(S): Wang, Shudong; Wood, Gavin; Duncan, Kenneth; Meades, Christopher; Gibson, Darron; Mclachlan, Janice; Fischer, Peter
PATENT ASSIGNEE(S): Cyclacel Limited, UK
SOURCE: PCT Int. Appl., 216 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005116025	A2	20051208	WO 2005-GB2134	20050526
WO 2005116025	A3	20060223		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-11791 A 20040526
OTHER SOURCE(S): MARPAT 144:36367

AB The present invention relates to 2-substituted 4-thiazolylpyrimidines (shown as I; variables defined below; e.g. (3-methylsulfonylphenyl)[4-(4- methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine (shown as II)), their preparation, pharmaceutical compns. containing them and their use as inhibitors of ≥1 protein kinases, and hence their use in the treatment of proliferative disorders, viral disorders and/or other disorders. For I: 1 of X1 and X2 is S, and the other is N; Z is NH, NHCO, NHCOCH2, NHSO2, NHCH2, CH2, CH2CH2, CH:CH, O, S, SO2, or SO; R1, R2, R3, R4, R5, R6, R7 and R8 = H, alkyl, alkyl-R9, aryl, aryl-R9, aralkyl, aralkyl-R9, halo, et al. or two of R4-R8 are linked to form a cyclic ether containing ≥1 oxygens; R9 = solubilizing group = mono, di- or polyhydroxylated alicyclic, di- or polyhydroxylated aliphatic or aromatic, carbohydrate derivative, O- and/or S-containing heterocyclic group, et al.; addnl. details including provisos are given in the claims. Protein kinase inhibition properties of many I for many kinases are tabulated. Although the methods of preparation are not claimed, prepns. and/or characterization data for 220 examples of I are included. For example, [4-(2-tert-butylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methyl-3-nitrophenyl)amine was prepared by condensation of 1-(2-tert-butylamino-4-methylthiazol-5-yl)-3-dimethylaminopropenone and N-(4-methyl-3-nitrophenyl)guanidine nitrate. Compds. I are also claimed useful in an assay for identifying further candidate compds. capable of inhibiting various enzymes.

IC ICM C07D417-00

28 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT Alopecia
Alzheimer's disease
Anti-AIDS agents
Anti-Alzheimer's agents
Antidiabetic agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Central nervous system, disease
Central nervous system agents
Cytotoxic agents
Diabetes mellitus
Drug delivery systems
Human
Human herpesvirus 1
Human herpesvirus 3
Human herpesvirus 5
Human immunodeficiency virus 1
Leukemia
Neoplasm
Psoriasis
Rheumatoid arthritis
(preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase inhibitors with improved solubility properties)

IT 870780-10-2P, 1-[4-[3-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870780-83-9P, 1-[4-[4-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870780-84-0P, 1-[4-[4-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870781-42-3P, N-[3-[[4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide
RL: BUU (Biological use, unclassified); **PAC (Pharmacological activity)**; RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase inhibitors with improved solubility properties)

IT 870780-07-7P, [3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]acetic acid 2-methoxyethyl ester 870780-08-8P, [4-(2-tert-Butylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methyl-3-nitrophenyl)amine 870780-11-3P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl](3-methylsulfonylphenyl)amine 870780-12-4P, N-[3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]methanesulfonamide 870780-15-7P, N-[3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]methanesulfonamide 870780-16-8P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl][3-(piperazin-1-yl)phenyl]amine 870780-17-9P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-(piperazin-1-yl)phenyl]amine 870780-18-0P, N-[3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]benzamide 870780-19-1P, N-[3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]-1,1,1-trifluoromethanesulfonamide 870780-20-4P, N-[3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]-1,1,1-trifluoromethanesulfonamide 870780-23-7P, N-[3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]-1,1,1-trifluoromethanesulfonamide 870780-24-8P, N-[4-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]acetamide 870780-26-0P, N-[4-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-

yl]amino]benzyl]acetamide 870780-27-1P, N-[4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]acetamide 870780-28-2P, N-[4-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]acetamide 870780-29-3P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methylsulfonylphenyl)amine 870780-30-6P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-31-7P, 3-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-32-8P, (4-Methylsulfonylphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870780-33-9P, N-Methyl-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-35-1P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-methylbenzenesulfonamide 870780-36-2P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870780-37-3P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870780-38-4P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870780-39-5P, 3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-methylbenzenesulfonamide 870780-40-8P, (3-Methylsulfonylphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870780-41-9P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](3-methylsulfonylphenyl)amine 870780-42-0P, N-Ethyl-3-[[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-44-2P, 3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-ethylbenzenesulfonamide 870780-45-3P, N-Ethyl-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-46-4P, N-(3-Methoxyphenyl)-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-49-7P, 3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-methylbenzenesulfonamide 870780-50-0P, 4-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-51-1P, 4-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-52-2P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-methyl-3-[(morpholin-4-yl)sulfonyl]phenyl]amine 870780-55-5P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl][4-methyl-3-[(morpholin-4-yl)sulfonyl]phenyl]amine 870780-56-6P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-methyl-3-[(morpholin-4-yl)sulfonyl]phenyl]amine 870780-57-7P, 4-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-58-8P, N-(2-Methoxyethyl)-4-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-59-9P, 4-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-60-2P, (3-Bromo-4-methylphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870780-63-5P, 4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-64-6P, [3-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]acetic acid 2-methoxyethyl ester 870780-65-7P, [3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]acetic acid 2-methoxyethyl ester 870780-66-8P, 1-[4-[3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870780-67-9P, [3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-5-hydroxymethylphenyl]methanol 870780-70-4P, [3-Hydroxymethyl-5-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]methanol 870780-71-5P, N-[3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]methanesulfonamide 870780-72-6P, (3-Bromophenyl)[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870780-75-9P, [4-(2-tert-Butylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](3-nitrophenyl)amine 870780-76-0P, N,N-Diethyl-4-[[4-(4-methyl-2-

methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-78-2P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-80-6P, N-(2-Methoxyethyl)-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-81-7P, 3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-82-8P, 3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-methoxyethyl)benzenesulfonamide 870780-85-1P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(piperazin-1-yl)phenyl]amine 870780-86-2P, [4-(4-Benzylpiperazin-1-yl)phenyl][4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870780-87-3P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(piperazin-1-yl)phenyl]amine 870780-88-4P, [3-[[[4-[[4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]sulfonyl]amino]phenyl]acetic acid ethyl ester 870780-90-8P, N-Acetyl-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-92-0P, N-Acetyl-3-[[4-(2-amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-93-1P, 4-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870780-95-3P, 4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-ethylbenzenesulfonamide 870780-97-5P, N-(2-Hydroxyethyl)-4-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870780-98-6P, 4-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870780-99-7P, 4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870781-00-3P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-isopropylbenzenesulfonamide 870781-02-5P, N-Benzyl-4-[[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870781-04-7P, N-Benzyl-4-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870781-05-8P, 4-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-benzylbenzenesulfonamide 870781-06-9P, N-Benzyl-4-[[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870781-07-0P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870781-09-2P, N-(2-Hydroxyethyl)-3-[[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870781-10-5P, 3-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870781-11-6P, 3-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870781-12-7P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][(pyridin-3-yl)methyl]amine 870781-13-8P, N-Benzyl-3-[[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]benzenesulfonamide 870781-15-0P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-[(morpholin-4-yl)sulfonyl]phenyl]amine 870781-17-2P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-methyl-3-[(morpholin-4-yl)sulfonyl]phenyl]amine 870781-18-3P, 3-[[4-[2-(2-Methoxyethylamino)-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzenesulfonamide 870781-20-7P, 3-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-N-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide 870781-22-9P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870781-23-0P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870781-24-1P, N-[5-(2-Aminopyrimidin-4-yl)-4-methylthiazol-2-yl]-N-ethylacetamide 870781-26-3P, [4-(2-Dimethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870781-27-4P, 4-Chloromethyl-N-[4-(2-dimethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]benzamide 870781-29-6P, (3-Aminomethylphenyl)[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870781-30-9P, Pyridine-2-carboxylic acid N-[3-[[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amino]benzyl]amide 870781-32-1P, 2-(4-Chlorophenyl)-N-[4-(2-dimethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]acetamide

870781-33-3P, N-[4-(2-Dimethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]-2-(4-nitrophenyl)acetamide 870781-34-3P, N-[4-(2-Dimethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]-2-(4-methoxyphenyl)acetamide 870781-35-4P, N-[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]-2-(4-methoxyphenyl)acetamide 870781-36-5P, N-[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]-2-(4-methoxyphenyl)acetamide 870781-37-6P, 2-(4-Chlorophenyl)-N-[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]acetamide 870781-38-7P, N-[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]-2-(4-nitrophenyl)acetamide 870781-39-8P, [4-[2-(2-Ethylpyridin-4-yl)-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-41-2P, [4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-43-4P, 4-[[4-[2-(2-Ethylpyridin-4-yl)-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]-N-(2-hydroxyethyl)benzenesulfonamide 870781-44-5P, N-[4-[[4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-45-6P, N-[4-[[4-[2-(2-Ethylpyridin-4-yl)-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-46-7P, N-[3-[[4-[2-(2-Ethylpyridin-4-yl)-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-47-8P, [4-[4-Methyl-2-(6-methylpyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-49-0P, [4-[2-[3-(2-Methoxyethoxy)-5-trifluoromethylpyridin-2-yl]-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-51-4P, N-[3-[[4-[4-Methyl-2-(6-methylpyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-52-5P, N-[3-[[4-[2-(3-Chloro-5-trifluoromethylpyridin-2-yl)-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-54-7P, N-(2-Methoxyethyl)-4-[[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amino]benzenesulfonamide 870781-56-9P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methoxy-2-methylphenyl)amine 870781-58-1P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl](4-methoxy-2-methylphenyl)amine 870781-59-2P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl](5-methoxy-2-methylphenyl)amine 870781-61-6P, [4-(4-Benzylpiperazin-1-yl)phenyl][4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870781-62-7P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](5-methoxy-2-methylphenyl)amine 870781-63-8P, (3-Aminomethylphenyl)[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870781-64-9P, [4-[2-[(Benzyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-66-1P, N-[3-[[4-[2-[(Benzyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-67-2P, 1-[4-[4-[[4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870781-68-3P, [4-[2-[(Ethyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-70-7P, [4-(2,6-Dimethylmorpholin-4-yl)phenyl][4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870781-72-9P, 1-[4-[4-[[4-[2-[(Benzyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870781-74-1P, [4-[2-[(3,5-Dichlorophenyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-76-3P, [4-[2-[(4-Chlorophenyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-78-5P, N-[3-[[4-[2-[(3,5-Dichlorophenyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-79-6P, [3,5-Dichloro-4-(morpholin-4-yl)phenyl][4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870781-81-0P, [3-Chloro-4-(morpholin-4-yl)phenyl][4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870781-82-1P, [3-Chloro-4-(morpholin-4-yl)phenyl][4-[2-[(3,5-dichlorophenyl)(methyl)amino]-4-methylthiazol-5-yl]pyrimidin-2-yl]amine 870781-83-2P, [4-[4-Methyl-2-(thiophen-2-yl)thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-84-3P, N-[3-[[4-[4-Methyl-2-(thiophen-2-yl)thiazol-5-yl]pyrimidin-2-yl]amino]benzyl]acetamide 870781-85-4P,

1-[4-[4-[[4-[4-Methyl-2-(thiophen-2-yl)thiazol-5-yl]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870781-86-5P, [5-[2-[(4-Dimethylaminophenyl)amino]pyrimidin-4-yl]-4-methylthiazol-2-yl]methanol 870781-89-8P, [3,5-Dichloro-4-(morpholin-4-yl)phenyl][4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870781-90-1P, [3-Chloro-4-(morpholin-4-yl)phenyl][4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870781-91-2P, [4-(4,2'-Dimethyl-[2,4']bithiazolyl-5-yl)pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-93-4P, [3-Chloro-4-(morpholin-4-yl)phenyl][4-(4,2'-dimethyl-[2,4']bithiazolyl-5-yl)pyrimidin-2-yl]amine 870781-94-5P, [3,5-Dichloro-4-(morpholin-4-yl)phenyl][4-(4,2'-dimethyl-[2,4']bithiazolyl-5-yl)pyrimidin-2-yl]amine 870781-95-6P, [4-[4-Methyl-2-[[(thien-2-yl)sulfonyl]methyl]thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870781-97-8P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][2-methyl-4-(morpholin-4-yl)phenyl]amine 870781-99-0P, [4-[2-(2,4-Dimethylphenyl)-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-01-7P, [3-Chloro-4-(morpholin-4-yl)phenyl][4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870782-02-8P, [3,5-Dichloro-4-(morpholin-4-yl)phenyl][4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870782-03-9P, [4-(2-tert-Butylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-04-0P, [4-[2-(2-Methoxyethylamino)-4-methylthiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-05-1P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl][2-methyl-4-(morpholin-4-yl)phenyl]amine 870782-06-2P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][2-methyl-4-(morpholin-4-yl)phenyl]amine 870782-07-3P, [4-[4-Methyl-2-[4-(morpholin-4-yl)phenyl]thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-09-5P, 1-[4-[4-[[4-[4-Methyl-2-[4-(morpholin-4-yl)phenyl]thiazol-5-yl]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870782-10-8P, N'-[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]-N-methyl-2-trifluoromethylbenzene-1,4-diamine 870782-12-0P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-[(morpholin-4-yl)methyl]phenyl]amine 870782-14-2P, 4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-2-[(morpholin-4-yl)methyl]phenol 870782-16-4P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-(morpholin-4-yl)phenyl]amine 870782-18-6P, [4-[4-Methyl-2-[(methyl)(pyridin-3-yl)amino]thiazol-5-yl]pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-20-0P, [4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870782-21-1P, (3,5-Dimethoxyphenyl)[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-22-2P, [3-Methoxy-4-(morpholin-4-yl)phenyl][4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-24-4P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methoxy-4-(morpholin-4-yl)phenyl]amine 870782-25-5P, [4-(4-Methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-27-7P, (3,5-Dimethoxyphenyl)[4-(4-methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-28-8P, (3,5-Dimethoxyphenyl)[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870782-29-9P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl](3,5-dimethoxyphenyl)amine 870782-30-2P, 1-[4-[4-[[4-(4-Methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870782-31-3P, 1-[4-[4-[[4-[4-Methyl-2-[(methyl)(pyridin-3-yl)amino]thiazol-5-yl]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870782-32-4P, [4-(4-Methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870782-33-5P, [4-(4-Benzylpiperazin-1-yl)phenyl][4-(4-methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-34-6P, [4-(4-Methyl-2-phenylaminothiazol-5-yl)pyrimidin-2-yl][4-(morpholin-4-yl)phenyl]amine 870782-36-8P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl](3,4,5-trimethoxyphenyl)amine 870782-37-9P, [4-(2,6-Dimethylmorpholin-4-yl)phenyl][4-(2-ethylamino-4-methylthiazol-5-

yl)pyrimidin-2-yl]amine [illegible] (3,5-Dimethoxyphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-39-1P, (3,5-Dimethoxyphenyl)[4-(4-methyl-2-phenylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-40-4P, 1-[4-[4-[[4-(4-Methyl-2-phenylaminothiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]ethanone 870782-41-5P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-methoxy-4-(morpholin-4-yl)phenyl]amine 870782-42-6P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-[(morpholin-4-yl)methyl]phenyl]amine 870782-44-8P, (3,5-Dimethoxyphenyl)[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amine 870782-45-9P, [4-(4-Benzylpiperazin-1-yl)phenyl][4-(4-methyl-2-phenylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-46-0P, (Benzodioxol-5-yl)[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-47-1P, (Benzodioxol-5-yl)[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870782-48-2P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl](benzodioxol-5-yl)amine 870782-49-3P, (2,3-Dihydrobenzo[1,4]dioxin-6-yl)[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-50-6P, (2,3-Dihydrobenzo[1,4]dioxin-6-yl)[4-(2-ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amine 870782-51-7P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methoxy-4-(morpholin-4-yl)phenyl]amine 870782-52-8P, (2,3-Dihydrobenzo[1,4]dioxin-6-yl)[4-(4-methyl-2-phenethylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-53-9P, (4-Methoxy-3-methylphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine 870782-55-1P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methoxy-3-methylphenyl)amine 870782-56-2P, (4-Methoxy-3-methylphenyl)[4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-57-3P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methoxy-3-methylphenyl)amine 870782-58-4P
, [4-Methyl-5-[2-[[4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]thiazol-2-yl]methanol 870782-59-5P, 4-[4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazine-1-carboxylic acid ethyl ester 870782-61-9P, 2-[4-[4-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]-N-isopropylacetamide 870782-63-1P, [4-(4-Methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl][4-(4-methylpiperazin-1-yl)phenyl]amine 870782-64-2P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-(piperidin-1-yl)phenyl]amine 870782-66-4P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(piperidin-1-yl)phenyl]amine 870782-67-5P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(piperidin-1-yl)phenyl]amine 870782-68-6P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(4-methylpiperazin-1-yl)phenyl]amine 870782-69-7P, [4-Methyl-5-[2-[[4-(piperidin-1-yl)phenyl]amino]pyrimidin-4-yl]thiazol-2-yl]methanol 870782-70-0P, [4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl][4-(pyrrolidin-1-yl)phenyl]amine 870782-72-2P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-(pyrrolidin-1-yl)phenyl]amine 870782-73-3P, [5-[2-[[3-Methoxy-4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]-4-methylthiazol-2-yl]methanol 870782-74-4P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(4-thiomorpholinyl)phenyl]amine 870782-76-6P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-(4-thiomorpholinyl)phenyl]amine 870782-77-7P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][4-(4-thiomorpholinyl)phenyl]amine 870782-78-8P, [4-[4-Methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl][4-(4-thiomorpholinyl)phenyl]amine 870782-79-9P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(piperidin-1-yl)phenyl]amine 870782-81-3P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(piperidin-1-yl)phenyl]amine 870782-82-4P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(piperidin-1-yl)phenyl]amine 870782-83-5P, [3-Methyl-4-(piperidin-1-yl)phenyl][4-[4-methyl-2-(pyridin-3-yl)thiazol-5-yl]pyrimidin-2-yl]amine 870782-84-6P, [4-Methyl-5-[2-[[3-methyl-4-(piperidin-1-yl)phenyl]amino]pyrimidin-4-yl]thiazol-2-yl]methanol 870782-85-7P,

5-[[4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl]amino]-2-(morpholin-4-yl)benzamide 870782-87-9P, 5-[[4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-2-(morpholin-4-yl)benzamide 870782-88-0P, 5-[[4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl]amino]-2-(morpholin-4-yl)benzamide 870782-89-1P, Cyclopropyl[4-[4-[[4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]methanone 870782-91-5P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-methyl-3-(morpholin-4-yl)phenyl]amine 870782-93-7P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][4-methoxy-3-[(morpholin-4-yl)methyl]phenyl]amine 870782-95-9P, [5-[2-[[3-Methoxy-4-(piperidin-1-yl)phenyl]amino]pyrimidin-4-yl]-4-methylthiazol-2-yl]methanol 870782-97-1P, [4-Methyl-5-[2-[[3-methyl-4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]thiazol-2-yl]methanol 870782-99-3P, [4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(morpholin-4-yl)phenyl]amine 870783-00-9P, [4-(2-Ethylamino-4-methylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(morpholin-4-yl)phenyl]amine 870783-01-0P, [4-(2,4-Dimethylthiazol-5-yl)pyrimidin-2-yl][3-methyl-4-(morpholin-4-yl)phenyl]amine
RL: BUU (Biological use, unclassified); **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase inhibitors with improved solubility properties)

IT 9059-09-0, Glycogen synthase kinase 80449-02-1, Tyrosine kinase **98037-52-6, Abelson tyrosine kinase** 101463-26-7 141349-86-2, CDK2 kinase 143375-65-9, CDK1 kinase 144378-32-5, Cyclin B-CDK1 kinase 146279-88-1, CDK2 cyclin A kinase 146279-89-2, CDK2 cyclin E kinase 147014-97-9, CDK4 kinase 147230-71-5, FLT-3 kinase 153190-71-7, CDK3 kinase 165245-99-8, Protein kinase PLK1 166433-53-0, CDK4 cyclin D1 kinase 182938-13-2, Protein kinase CDK9 195740-69-3, Aurora B kinase 303014-92-8, CDK6 kinase 372092-80-3, Protein kinase 386705-49-3, VEGF receptor tyrosine kinase 403652-37-9, CDK8 kinase 425381-48-2, CDK9 cyclin T1 protein kinase 444018-21-7, Aurora C kinase 458560-40-2, Aurora A kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase **inhibitors** with improved solubility properties)

L66 ANSWER 7 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:729564 HCAPLUS Full-text
DOCUMENT NUMBER: 143:186693
TITLE: Compositions and methods of use for tyrosine kinase inhibitors to treat pathogenic infection
INVENTOR(S): Kalman, Daniel; Bornmann, William Gerard; Sherman, Melanie Anne; Reeves, Patrick Michael; Swimm, Alyson Irene
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005072826	A2	20050811	WO 2005-US1710	20050120
WO 2005072826	A3	20060420		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

AU 2005209231 A1 20050811 AU 2005-209231 20050120
PRIORITY APPLN. INFO.: US 2004-537960P P 20040121
US 2004-553681P P 20040316
US 2004-614203P P 20040929
WO 2005-US1710 W 20050120

OTHER SOURCE(S): MARPAT 143:186693

AB Compns. and methods are provided for using tyrosine kinase inhibitors to treat pathogenic infection. In particular, methods for using **Abl** family tyrosine **kinase inhibitors** to treat pathogenic infection are provided. Infections to be treated according to the invention include, particularly, those caused by microbial pathogens such as bacteria and viruses.

IC ICM A61P031-04
ICS A61P031-12; A61K031-506; A61K031-519; A61K031-517

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

ST pathogen infection treatment tyrosine kinase inhibitor; **Abl** family tyrosine **kinase inhibitor** pathogen infection treatment; bacterial virus infection treatment tyrosine kinase inhibitor

IT **Escherichia coli**
(**enteropathogenic**; tyrosine kinase inhibitors for treatment of pathogenic infection)

IT **Antibacterial agents**
Antitumor agents
Antiviral agents
BK virus
Blood analysis
Chronic myeloid leukemia
Cytomegalovirus
Escherichia coli
Helicobacter pylori
Herpesviridae
Human
Human herpesvirus
Human immunodeficiency virus
Human immunodeficiency virus 1
JC virus
Listeria monocytogenes
Mycobacterium tuberculosis
Polyomavirus
Prophylaxis
Salmonella typhimurium
Shigella flexneri
Tuberculostatics
Vaccinia virus
Variola virus
(tyrosine kinase inhibitors for treatment of pathogenic infection)

IT **98037-52-6**, Abl tyrosine **kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**abl** family tyrosine **kinase**; tyrosine kinase **inhibitors** for treatment of pathogenic infection)

IT 185039-91-2, PD166326
RL: ANT (Analyte); PAC (**Pharmacological activity**); THU

(Therapeutic use); ANST (Analytical study); BIOL (Biological study);
USES (Uses)
(tyrosine kinase inhibitors for treatment of pathogenic infection)

IT 254-61-5D, Pyrido[2,3-d]pyrimidine, derivs. 152459-95-5 152459-95-5D, derivs. 183321-74-6, Erlotinib 184475-35-2, Gefitinib 185039-96-7, SKI DV 2-89 212142-18-2 212391-57-6, SKI DV2-47 220127-57-1, Imatinib mesylate 220127-57-1D, Imatinib mesylate, derivs. 252003-65-9, CP-547632 260415-63-2, PD173955 287204-45-9, PD180970 302962-49-8, BMS354825 305820-75-1, PD173952 305820-76-2, PD173956 305820-77-3, PD173958 341031-54-7, SU011248 443913-73-3, ZD-6474 557795-19-4, SU11248 593281-61-9, STI-X 593281-61-9D, derivs. 648903-75-7, SKI DV-M016 648903-76-8, SKI DV2-43 648903-77-9, SKI DV1-10 648903-78-0, SKI DV-M 017 648903-79-1, SKI DV2-87 730961-22-5, SKI DV 1-28 730977-96-5, SKI DV 2-33 730978-02-6, SKI DV2-53 730978-37-7, SKI DV 2-35 730978-44-6, SKI DV2-71 862110-19-8, SKI DV 2-45
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors for treatment of pathogenic infection)

L66 ANSWER 8 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:260034 HCAPLUS Full-text
DOCUMENT NUMBER: 142:336376
TITLE: Preparation of pharmaceutically active 4,6-disubstituted aminopyrimidine derivatives as modulators of protein kinases
INVENTOR(S): Choidas, Axel; Backes, Alexander; Cotten, Matt; Engkvist, Ola; Felber, Beatrice; Freisleben, Achim; Godl, Klaus; Greff, Zoltan; Habenberger, Peter; Hafenbradl, Doris; Hartung, Christian; Herget, Thomas; Hoppe, Edmund; Klebl, Bert; Missio, Andrea; Mueller, Gerhard; Schwab, Wilfried; Zech, Birgit; Bravo, Jose; Harris, John; Le, Joelle; Macritchie, Jackie; Savic, Vladimir; Sherborne, Brad; Simpson, Don; Simpson, Don
PATENT ASSIGNEE(S): Axxima Pharmaceuticals AG, Germany
SOURCE: PCT Int. Appl., 211 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005026129	A1	20050324	WO 2004-EP10353	20040915
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1678147	A1	20060712	EP 2004-786953	20040915
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: EP 2003-20888 A 20030915

...phenyl]amide	US 2003-504527P	P	20030922
	EP 2004-10308	A	20040430
	US 2004-569806P	P	20040512
	WO 2004-EP10353	W	20040915

OTHER SOURCE(S): MARPAT 142:336376

AB The invention is related to the preparation of title compds. I, and/or stereoisomeric forms and/or pharmaceutically acceptable salts [wherein R1 = H, (un)substituted alk(en/yn)yl; R2, R4 = independently H, F, Cl, Br, I, CN, NH2, NO2, (un)substituted alk(en/yn)yl; R3 = F, Cl, Br, I, (un)substituted hetero/aryl, etc.; X = R5-[LR6]m; R5 = (un)substituted hetero/aryl, heterocyclyl, cycloalkyl, etc.; R6 = H, (un)substituted alkyl, hetero/aryl, heterocyclyl, etc.; L = NRSO2, NRSO; R = H, (un)substituted alkyl, SO2-alkyl, etc.] as protein kinase inhibitors for use in the prophylaxis and/or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunol. diseases, autoimmune diseases, bipolar and clin. disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke. The invention is also related to a medium comprising at least one of compds. I in an immobilized form and its use for enriching, purifying and/or depleting nucleotide binding proteins which bind to the immobilized I. General preparation procedures and 5 individual synthetic examples are given. I have an inhibitory effect on the protein kinase activity of various protein kinases, such as Abl, CDK1, CDK5, etc. Selected I had an inhibitory effect on CDK9 and CDK2 with IC50 values in the range of 1 to 1000 nM. I were potent inhibitors of HIV and HCMV replication in cell cultures; for example II showed inhibition of HCMV replication in HFF cells.

IC ICM C07D239-42
ICS C07D401-12; C07D239-48; C07D403-12; C07D401-04; C07D409-12; C07D417-12; C07D405-12; C07D409-14; C07D413-12; C07D409-04; A61K031-505

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7, 63

IT Anti-infective agents
Anti-inflammatory agents
Antidiabetic agents
Antipsychotics
Antiviral agents
Anxiety
Anxiolytics
Autoimmune disease
Cardiovascular agents
Cardiovascular system, disease
Cytotoxic agents
Diabetes mellitus
Human
Human immunodeficiency virus 1
Immune disease
Immunomodulators
Infection
Inflammation
Prion diseases
Transplant rejection
(pharmaceutically active 4,6-disubstituted aminopyrimidine derivs. as modulators of protein kinases)

IT 848636-28-2P 848636-35-1P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]benzene-1,4-diamine
RL: **PAC (Pharmacological activity)**; RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of 4,6-disubstituted aminopyrimidines as

(modulators of protein kinases)

IT 848636-14-6P, N-[4-[6-(4-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-4-methylbenzenesulfonamide 848636-15-7P, N-[4-[6-(3-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-4-methylbenzenesulfonamide 848636-16-8P, N-[5-[6-(4-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848636-17-9P, 4-Amino-N-[4-[[6-(2-benzyloxyphenyl)pyrimidin-4-yl]amino]phenyl]benzamide 848636-18-0P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-4-methylbenzenesulfonamide 848636-19-1P, 4-Amino-N-[4-[6-(4-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-20-4P, [6-(2-Benzyloxyphenyl)pyrimidin-4-yl][2-(pyridin-4-yl)ethyl]amine 848636-21-5P, 4-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-22-6P, 1-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]pyrrolidin-2-one 848636-23-7P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]acetamide 848636-24-8P, N-[4-[6-(4-Hydroxyphenyl)pyrimidin-4-ylamino]phenyl]-4-methylbenzenesulfonamide 848636-25-9P, N-[5-[6-(3-Aminophenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848636-26-0P, [6-(3-Aminophenyl)pyrimidin-4-yl][2-(pyridin-4-yl)ethyl]amine 848636-27-1P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzamide 848636-29-3P, 4-Amino-N-[4-[6-(4-hydroxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-30-6P 848636-31-7P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-4-methyl-N-propylbenzenesulfonamide 848636-32-8P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2,2-dimethylpropionamide 848636-33-9P, 2-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-34-0P, 4-Amino-N-[4-[6-(3-aminophenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-36-2P, 4-Isopropyl-N-[4-[6-(2-methoxyphenyl)pyrimidin-1-ylamino]phenyl]benzenesulfonamide 848636-37-3P, N-[4-(6-Chloropyrimidin-4-ylamino)phenyl]-4-methylbenzenesulfonamide 848636-38-4P, 4-Amino-N-[4-(6-chloropyrimidin-4-ylamino)phenyl]benzamide 848636-39-5P, N-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-methylbenzene-1,4-diamine 848636-40-8P, [[4-[6-(4-Hydroxyphenyl)pyrimidin-4-ylamino]phenyl](4-tolylsulfonyl)amino]acetic acid methyl ester 848636-41-9P, [[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl](4-tolylsulfonyl)amino]acetic acid methyl ester 848636-42-0P, (S)-2-[[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]carbamoyl]piperidine-1-carboxylic acid tert-butyl ester 848636-43-1P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-44-2P, 4-Amino-N-[4-[6-(2,4-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-45-3P, 4-Amino-N-[4-(6-styrylpyrimidin-4-ylamino)phenyl]benzamide 848636-46-4P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]methanesulfonamide 848636-47-5P, Biphenyl-4-sulfonic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-48-6P, 4-Amino-N-[4-[6-(5-isopropyl-2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-49-7P, Bicyclo[2.2.1]heptane-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-50-0P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-3-methyl-2-phenylbutyramide 848636-51-1P, 1-Cyclohexyl-3-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]urea 848636-52-2P, 4-Amino-N-[4-[6-(5-chloro-2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-53-3P, (E)-3-[3-[6-[[4-[(4-Tolylsulfonyl)amino]phenyl]amino]pyrimidin-4-yl]phenyl]-2-propenoic acid 848636-54-4P, Cyclohexanecarboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-55-5P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-3,3-dimethylbutyramide 848636-56-6P, 4-Amino-N-[4-[[6-[(cyclohexylmethyl)amino]pyrimidin-4-yl]amino]phenyl]benzamide 848636-57-7P, N-Cyclohexyl-4-[[6-(2-methoxyphenyl)pyrimidin-4-

ylamino]benzamide 848636-58-8P, 4-tert-Butyl-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-59-9P, 2-Dimethylamino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]acetamide 848636-60-2P 848636-61-3P, 2-[[[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]carbamoyl]methyl]piperidine-1-carboxylic acid tert-butyl ester 848636-62-4P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-4-(4-methylpiperazin-1-yl)benzamide 848636-63-5P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]isonicotinamide 848636-64-6P, 4-Amino-N-[4-[6-(2,6-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-65-7P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-phenylbenzamide 848636-66-8P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]guanidine 848636-67-9P, N-tert-Butyl-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzamide 848636-68-0P, 4-Amino-N-[4-[6-(2-ethoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-69-1P, 4-Amino-N-[4-[6-(2,3-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-70-4P, 4-Amino-N-[4-[6-(2,5-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-71-5P, 4-Amino-N-[4-[6-(2-isopropoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848636-72-6P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-(piperidin-2-yl)acetamide 848636-73-7P, 4-Amino-N-[4-[[6-(2-hydroxyethylamino)pyrimidin-4-yl]amino]phenyl]benzamide 848636-74-8P, Adamantane-1-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-75-9P, [4-(Benzoxazol-2-yl)phenyl][6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848636-76-0P, [4-(1H-Benzimidazol-2-yl)phenyl][6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848636-77-1P, 3-Diethylamino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]propionamide 848636-78-2P, (S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid N-[4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]phenyl]amide 848636-79-3P, 1-Aminocyclohexanecarboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-80-6P, 4-Amino-N-[4-[6-(pyridin-4-yl)pyrimidin-4-ylamino]phenyl]benzamide 848636-81-7P, 1-Aminocyclopentanecarboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-82-8P, (R)-Piperidine-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-83-9P 848636-84-0P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-phenylacetamide 848636-85-1P, N-[4-(6-Chloropyrimidin-4-ylamino)phenyl]-2,2-dimethylpropionamide 848636-86-2P, 2,2-Dimethyl-N-[4-[6-(pyridin-3-yl)pyrimidin-4-ylamino]phenyl]-1-propionamide 848636-87-3P, 2,2-Dimethyl-N-[4-[[6-(1-methylpiperidin-4-ylamino)pyrimidin-4-yl]amino]phenyl]propionamide 848636-88-4P, 3-[6-[[4-(2,2-Dimethylpropionylamino)phenyl]amino]pyrimidin-4-yl]benzoic acid 848636-89-5P, 4-Amino-N-[4-(6-phenylpyrimidin-4-ylamino)phenyl]benzamide 848636-90-8P, 4-Amino-N-[4-[6-(thiophen-2-yl)pyrimidin-4-ylamino]phenyl]benzamide 848636-91-9P, 2,2-Dimethyl-N-[4-[[6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl]amino]phenyl]propionamide 848636-92-0P, N-[4-[[6-(2-Aminoethylamino)pyrimidin-4-yl]amino]phenyl]-2,2-dimethylpropionamide 848636-93-1P, N-[4-[[6-(3-Hydroxypropylamino)pyrimidin-4-yl]amino]phenyl]-2,2-dimethylpropionamide 848636-94-2P, (S)-2-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-phenylethanamide 848636-95-3P, (S)-N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-methylamino-2-phenylethanamide 848636-96-4P 848636-97-5P, Benzothiazole-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848636-98-6P, N-[4-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]phenyl]-2,2-dimethylpropionamide 848636-99-7P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-(piperidin-3-yl)benzamide 848637-00-3P, 1-Methylpiperidine-3-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-01-4P, 4-(6-Chloropyrimidin-4-ylamino)-N-cyclohexylbenzamide

848637-02-5P, 1-Methylpiperidine-4-carboxylic acid N-[4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]phenyl]amide 848637-03-6P, (S)-Azetidine-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-04-7P, (R)-Pyrrolidine-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-05-8P, [6-(4-Methoxyphenyl)pyrimidin-4-yl][2-(pyridin-4-yl)ethyl]amine 848637-06-9P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][2-(pyridin-4-yl)ethyl]amine 848637-07-0P, 2-[6-[[2-(Pyridin-4-yl)ethyl]amino]pyrimidin-4-yl]phenol 848637-08-1P, 4-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]benzamide 848637-09-2P, N-[4-[[6-(2-Methoxyphenyl)pyrimidin-4-yl](methyl)amino]phenyl]-4-methylbenzenesulfonamide 848637-10-5P, 4-Amino-N-[4-[2-amino-6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848637-11-6P, Quinoline-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-12-7P, [6-(2-Isopropoxyphenyl)pyrimidin-4-yl][2-(pyridin-4-yl)ethyl]amine 848637-13-8P, N-[5-[6-(3-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-14-9P, 2-Dimethylamino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-phenylacetamide 848637-15-0P, 3-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]propionamide 848637-16-1P, 4-Amino-N-[4-[[6-[2-(3-aminopropoxy)phenyl]pyrimidin-4-yl]amino]phenyl]benzamide 848637-17-2P, N-[3-[6-[[3-[(Methylsulfonyl)amino]-4-methylphenyl]amino]pyrimidin-4-yl]phenyl]acetamide 848637-18-3P, N-[5-[6-(3-Hydroxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-19-4P, N-[2-Methyl-5-(6-phenylpyrimidin-4-ylamino)phenyl]methanesulfonamide 848637-20-7P, N-[2-Methyl-5-[6-(3-trifluoromethylphenyl)pyrimidin-4-ylamino]phenyl]methanesulfonamide 848637-21-8P, N-[5-[[6-[3-[(Methylsulfonyl)amino]phenyl]pyrimidin-4-yl]amino]-2-methylphenyl]methanesulfonamide 848637-22-9P, N-[5-[6-(3-Aminophenyl)pyrimidin-4-ylamino]-2-methylphenyl]benzenesulfonamide 848637-23-0P, N-[5-([4,5']Bipyrimidinyl-6-ylamino)-2-methylphenyl]methanesulfonamide 848637-24-1P, 1-(Benzodioxol-5-yl)-3-[4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]phenyl]urea 848637-25-2P, 1-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-3-(4-methylbenzyl)urea 848637-26-3P, 1-tert-Butyl-3-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]urea 848637-27-4P, 2,2-Dimethyl-N-[4-[6-(2-trifluoromethylphenyl)pyrimidin-4-ylamino]phenyl]propionamide 848637-28-5P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzamide 848637-29-6P, Propane-1-sulfonic acid N-[5-[6-(3-aminophenyl)pyrimidin-4-ylamino]-2-methylphenyl]amide 848637-30-9P, 4-[6-(3-Aminophenyl)pyrimidin-4-ylamino]benzenesulfonamide 848637-31-0P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-methyl-2-methylaminopropionamide 848637-32-1P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-3-methylphenyl]-2,2-dimethylpropionamide 848637-33-2P, N-[5-[6-(3-Aminophenyl)pyrimidin-4-ylamino]-2-benzyloxyphenyl]methanesulfonamide 848637-34-3P, N-[3-[6-(3-Aminophenyl)pyrimidin-4-ylamino]phenyl]methanesulfonamide 848637-35-4P, N-[3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2,2-dimethylpropionamide 848637-36-5P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]-2-methylbenzene-1,4-diamine 848637-37-6P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]benzene-1,3-diamine 848637-38-7P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-[4-(morpholin-4-yl)phenyl]benzamide 848637-39-8P, 2,2-Dimethyl-N-[4-[6-(2-vinylphenyl)pyrimidin-4-ylamino]phenyl]propionamide 848637-40-1P, N-[4-[6-(2-Fluorophenyl)pyrimidin-4-ylamino]phenyl]-2,2-dimethylpropionamide 848637-41-2P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-42-3P, 2-Oxo-2H-chromene-3-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-

ylamino]phenyl]amide 848637-43-4P, Benzodioxole-5-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-44-5P, N-[4-[6-(2-Ethylphenyl)pyrimidin-4-ylamino]phenyl]-2,2-dimethylpropionamide 848637-45-6P, N-[4-[6-(Biphenyl-2-yl)pyrimidin-4-ylamino]phenyl]-2,2-dimethylpropionamide 848637-46-7P, 1H-Indole-3-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-47-8P 848637-48-9P, N-(4-Hydroxyphenyl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzamide 848637-49-0P, N-(4-Isopropylphenyl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzamide 848637-50-3P, 1H-Benzimidazole-5-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-51-4P, 1-Hydroxynaphthalene-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-52-5P, (2S,3S)-2-Amino-3-methylpentanoic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-53-6P, 1H-Indazole-3-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-54-7P, Quinoline-8-sulfonic acid N-[5-[6-(3-aminophenyl)pyrimidin-4-ylamino]-2-methylphenyl]amide 848637-55-8P, (S)-2-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]-3-methylbutanamide 848637-56-9P, 1-Methyl-1H-imidazole-4-sulfonic acid N-[5-[6-(3-aminophenyl)pyrimidin-4-ylamino]-2-methylphenyl]amide 848637-57-0P, 3-Hydroxynaphthalene-2-carboxylic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-58-1P, 2-Amino-N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]-2-(naphthalen-2-yl)acetamide 848637-59-2P, [4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]morpholin-4-ylmethanone 848637-60-5P 848637-61-6P, 4-Amino-N-[4-[6-(2-methoxyphenyl)-5-methylpyrimidin-4-ylamino]phenyl]benzamide 848637-62-7P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848637-63-8P, 4-Amino-N-[4-[6-(2-hydroxyphenyl)pyrimidin-4-ylamino]phenyl]benzamide 848637-64-9P, N-[6-(2-Methoxyphenyl)-5-methylpyrimidin-4-yl]benzene-1,4-diamine 848637-65-0P, Propane-2-sulfonic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-66-1P, Propane-1-sulfonic acid N-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-67-2P, N-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]benzenesulfonamide 848637-68-3P, N-[5-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]-2-methylphenyl]methanesulfonamide 848637-69-4P, N-[5-[[6-(3-Dimethylaminophenyl)pyrimidin-4-yl]amino]-2-methylphenyl]methanesulfonamide 848637-70-7P, N-[5-[6-(2-Isopropoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-71-8P 848637-72-9P, Propane-1-sulfonic acid N-[4-[6-(2-methoxyphenyl)-5-methylpyrimidin-4-ylamino]phenyl]amide 848637-73-0P, N-(2-Aminocyclohexyl)-4-[[6-(4-methoxyphenyl)pyrimidin-4-yl]amino]benzamide 848637-74-1P, N-[5-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-75-2P, N-[5-[6-(3-Cyanophenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-76-3P, (S)-Piperidine-2-carboxylic acid N-[3-[[6-(2-benzyloxyphenyl)pyrimidin-4-yl]amino]phenyl]amide 848637-77-4P, N-[5-[6-(3-Formylphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-78-5P, N-[5-[6-(2-Hydroxymethylphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-79-6P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(4-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-80-9P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(3-formylphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-81-0P, (S)-Piperidine-2-carboxylic acid N-[3-[[6-(3-dimethylaminophenyl)pyrimidin-4-yl]amino]phenyl]amide 848637-82-1P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(2-hydroxymethylphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-83-2P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(2-methoxypyridin-3-yl)pyrimidin-4-ylamino]phenyl]amide 848637-84-3P, (S)-Piperidine-2-carboxylic acid

N-[3-[6-(2-Methoxypyridin-3-yl)pyrimidin-4-ylamino]phenyl]amide 848637-85-4P, (S)-Piperidine-2-carboxylic acid N-[3-[[6-(4-benzyloxyphenyl)pyrimidin-4-yl]amino]phenyl]amide 848637-86-5P, (S)-Piperidine-2-carboxylic acid N-[3-[6-(4-phenoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-87-6P, N-[5-[6-(4-Hydroxymethylphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-88-7P, N-[5-[6-(2-Methoxypyridin-3-yl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-89-8P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(4-acetylaminophenyl)pyrimidin-4-ylamino]phenyl]amide 848637-90-1P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-[3-[(methylsulfonyl)amino]phenyl]pyrimidin-4-yl]amino]phenyl]amide 848637-91-2P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(3-acetylphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-92-3P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-[4-(cyclopentylcarbamoyl)phenyl]pyrimidin-4-yl]amino]phenyl]amide 848637-93-4P, N-[5-[6-(2-Hydroxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-94-5P, (E)-3-[3-[6-[[3-[(Methylsulfonyl)amino]-4-methylphenyl]amino]pyrimidin-4-yl]phenyl]-2-propenoic acid methyl ester 848637-95-6P, N-[5-[6-(3-Hydroxymethylphenyl)pyrimidin-4-ylamino]-2-methylphenyl]methanesulfonamide 848637-96-7P, N-Butyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848637-97-8P, (3-Methylsulfonylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848637-98-9P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2,3-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848637-99-0P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2,4-dimethoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848638-00-6P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2-isopropoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848638-01-7P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-(2-methylsulfanylphenyl)pyrimidin-4-yl]amino]phenyl]amide 848638-02-8P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2-trifluoromethoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848638-03-9P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-[5-(acetyl)thiophen-2-yl]pyrimidin-4-yl]amino]phenyl]amide 848638-04-0P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(2-chlorophenyl)pyrimidin-4-ylamino]phenyl]amide 848638-05-1P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(3-hydroxymethylphenyl)pyrimidin-4-ylamino]phenyl]amide 848638-06-2P 848638-07-3P 848638-08-4P 848638-09-5P, N-[5-[[6-(2-Methoxymethylphenyl)pyrimidin-4-yl]amino]-2-methylphenyl]methanesulfonamide 848638-10-8P 848638-11-9P 848638-12-0P, 4-Amino-N-[4-[6-(4-methoxyphenyl)-5-methylpyrimidin-4-ylamino]phenyl]benzamide 848638-13-1P 848638-14-2P, (S)-Piperidine-2-carboxylic acid N-[4-[6-(4-methoxyphenyl)pyrimidin-4-ylamino]phenyl]amide 848638-15-3P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-(3-methoxymethylphenyl)pyrimidin-4-yl]amino]phenyl]amide 848638-16-4P, N-[6-(2-Methoxyphenyl)-2-methylpyrimidin-4-yl]benzene-1,4-diamine 848638-17-5P, N-[6-(4-Methoxyphenyl)-2-methylpyrimidin-4-yl]benzene-1,4-diamine 848638-18-6P 848638-19-7P 848638-20-0P 848638-21-1P 848638-22-2P 848638-23-3P, (S)-Piperidine-2-carboxylic acid N-[4-[[6-[3-[(dimethylamino)methyl]phenyl]pyrimidin-4-yl]amino]phenyl]amide 848638-24-4P 848638-25-5P 848638-26-6P, 3-[6-(3-Aminophenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-27-7P, 3-[6-(4-Methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-28-8P, N-((R,R)-2-Aminocyclohexyl)-4-[[6-(2-hydroxymethylphenyl)pyrimidin-4-yl]amino]benzamide 848638-29-9P, N-(2-Diethylaminoethyl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzamide 848638-30-2P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-(2-hydroxyphenyl)pyrimidin-4-yl]amino]benzamide 848638-31-3P 848638-32-4P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-[5-[(dimethylamino)methyl]pyridin-3-yl]pyrimidin-4-yl]amino]benzamide 848638-33-5P, (R,R)-5-[6-[[4-(2-Aminocyclohexylcarbamoyl)phenyl]amino]pyrimidin-4-yl]pyridine-2-carboxylic acid dimethylamide 848638-34-6P,

(R,R)-N-(2-Aminocyclohexyl)-4-[[6-(6-methylsulfanylpyridin-3-yl)pyrimidin-4-yl]amino]benzamide 848638-35-7P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-(5-aminomethylpyridin-3-yl)pyrimidin-4-yl]amino]benzamide 848638-36-8P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-(4-methylsulfanylpyridin-3-yl)pyrimidin-4-yl]amino]benzamide 848638-37-9P, N-(2-Aminocyclohexyl)-4-[[6-(5-hydroxymethylpyridin-3-yl)pyrimidin-4-yl]amino]benzamide 848638-38-0P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-(pyrrolidin-3-yl)benzamide 848638-39-1P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-(5-dimethylaminopyridin-3-yl)pyrimidin-4-yl]amino]benzamide 848638-40-4P, (R,R)-4-[[6-[5-(Acetyl)thiophen-2-yl]pyrimidin-4-yl]amino]-N-(2-aminocyclohexyl)benzamide 848638-41-5P 848638-42-6P, (R,R)-4-[6-(2-Acetylphenyl)pyrimidin-4-ylamino]-N-(2-aminocyclohexyl)benzamide 848638-43-7P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-(pyridin-3-yl)benzamide 848638-44-8P, N-(1-Acetylpiperidin-3-yl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzamide 848638-45-9P, (R,R)-N-(2-Aminocyclohexyl)-4-[[6-(2-dimethylaminophenyl)pyrimidin-4-yl]amino]benzamide 848638-46-0P 848638-47-1P, 2-Chloro-5-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-48-2P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][3-[(piperidin-1-yl)sulfonyl]phenyl]amine 848638-49-3P, N-Allyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 4,6-disubstituted aminopyrimidines as modulators of protein kinases)

IT 848638-50-6P, N-Benzyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-51-7P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][3-[(pyrrolidin-1-yl)sulfonyl]phenyl]amine 848638-52-8P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][3-[(morpholin-4-yl)sulfonyl]phenyl]amine 848638-53-9P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-methylbenzenesulfonamide 848638-54-0P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]-N-(3-sulfamoylphenyl)acetamide 848638-55-1P, N,N-Diallyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-56-2P, 3-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848638-57-3P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][4-(4-nitrophenylsulfonyl)phenyl]amine 848638-58-4P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](4-trifluoromethylsulfonylphenyl)amine 848638-59-5P, (4-Methylsulfonylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-60-8P, N-(3,4-Dimethylisoxazol-5-yl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848638-61-9P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-propylbenzenesulfonamide 848638-62-0P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848638-63-1P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N,N-dimethylbenzenesulfonamide 848638-64-2P, N-(2-Methoxyethyl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848638-65-3P, [6-(2-Benzyloxyphenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848638-66-4P, 2-[6-[(3-Methylsulfonylphenyl)amino]pyrimidin-4-yl]phenol 848638-67-5P, [6-(3-Aminophenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848638-68-6P, 5-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylbenzenesulfonic acid 848638-69-7P, 2-[[3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]sulfonyl]ethanol 848638-70-0P, (2-Fluoro-5-methylsulfonylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-71-1P, [6-(2-Aminophenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848638-72-2P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](3-trifluoromethylsulfonylphenyl)amine 848638-73-3P, (3-Methylsulfonylphenyl)[6-(2-Phenoxyphenyl)pyrimidin-4-yl]amine 848638-74-4P, [6-(2-Butoxyphenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848638-75-5P, (3-Ethenylsulfonylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-76-6P, (S)-Piperidine-2-

carboxylic acid N-[4-[[6-(4-methylsulfanylphenyl)pyrimidin-4-yl]amino]phenyl]amide 848638-77-7P, 2-Chloro-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848638-78-8P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](4-phenoxybenzyl)amine 848638-79-9P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-3-methylbenzoic acid methyl ester 848638-80-2P, [6-(3-Aminophenyl)pyrimidin-4-yl](1-methylsulfonyl-2,3-dihydro-1H-indol-6-yl)amine 848638-81-3P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]piperidine-1-carboxylic acid tert-butyl ester 848638-82-4P 848638-83-5P, (1H-Indazol-6-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-84-6P, 1-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]butan-1-one 848638-85-7P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](piperidin-3-yl)amine 848638-86-8P, [4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]phenylmethanone 848638-87-9P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]-N'-phenylbenzene-1,3-diamine 848638-88-0P, [3-([1,3]Dioxan-2-yl)phenyl][6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-89-1P, (3-Methoxyphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-90-4P, (4-Methoxyphenyl)[6-(2-Methoxyphenyl)pyrimidin-4-yl]amine 848638-91-5P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]-N'-phenylbenzene-1,4-diamine 848638-92-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][4-(morpholin-4-yl)phenyl]amine 848638-93-7P, (2-Fluorophenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-94-8P, (1-Benzylpiperidin-4-yl)[6-(2-Methoxyphenyl)pyrimidin-4-yl]amine 848638-95-9P, (4-Butylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848638-96-0P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](4-phenoxyphenyl)amine 848638-97-1P, 4-[[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]methyl]benzenesulfonamide 848638-98-2P, 1-Dimethylamino-3-[4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]phenoxy]-3-propan-2-ol 848638-99-3P, N-[6-(4-Methoxyphenyl)-5-methylpyrimidin-4-yl]benzene-1,4-amine 848639-00-9P, N-[6-(3-Aminophenyl)-5-methylpyrimidin-4-yl]benzene-1,4-amine 848639-01-0P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](piperidin-4-yl)amine 848639-02-1P, 4-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]piperidine-1-carboxylic acid tert-butyl ester 848639-03-2P, Cyclohexyl[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-04-3P, 4-[[6-[2-[2-(Morpholin-4-yl)ethoxy]phenyl]pyrimidin-4-yl]amino]benzoic acid methyl ester 848639-05-4P, 2-Methoxy-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848639-06-5P, [4-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]phenyl]acetic acid 848639-07-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](3-nitrophenyl)amine 848639-08-7P, [3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]methanol 848639-09-8P, N-[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]phenylamine 848639-10-1P, N-[6-(2-Methoxyphenyl)pyrimidin-4-yl]phenylamine 848639-11-2P, (4-Fluorophenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-12-3P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](3-phenoxyphenyl)amine 848639-13-4P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](3-methylsulfanylphenyl)amine 848639-14-5P, [6-(2-Benzyloxyphenyl)pyrimidin-4-yl](piperidin-4-yl)amine 848639-15-6P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenol 848639-16-7P, 1-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]ethanone 848639-17-8P, 2-Chloro-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid 848639-18-9P, [4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]butyl]carbamic acid tert-butyl ester 848639-19-0P, [6-(2-Benzyloxyphenyl)pyrimidin-4-yl](1-methylsulfonyl-2,3-dihydro-1H-indol-6-yl)amine 848639-20-3P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]piperidine-1-carboxylic acid tert-butyl ester 848639-21-4P, 4-[6-(2-Aminophenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848639-22-5P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](4-methylsulfanylphenyl)amine 848639-23-6P 848639-24-7P, 1-[4-[[6-(2-Benzyloxyphenyl)pyrimidin-4-yl]amino]phenoxy]-3-dimethylaminopropan-2-ol 848639-25-8P, (1-Methylsulfonyl-2,3-dihydro-1H-indol-6-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-26-9P,

N-(2-Aminocyclohexyl)-4-[[6-[(Benzotriazol-1-yl)oxy]pyrimidin-4-yl]amino]benzamide 848639-27-0P, [2-[4-[[6-[(Benzotriazol-1-yl)oxy]pyrimidin-4-yl]amino]benzoylamino]cyclohexyl]carbamic acid tert-butyl ester 848639-28-1P, 1-[3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]ethanone 848639-29-2P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][4-(piperidin-1-yl)phenyl]amine 848639-30-5P, 3-Hydroxy-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848639-31-6P, 2-Hydroxy-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848639-32-7P, 4-Aminobutane-1-sulfonic acid N-[5-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]amide 848639-33-8P, [3-[6-[[3-(4-Aminobutan-1-ylsulfonylamino)-4-methylphenyl]amino]pyrimidin-4-yl]phenyl]carbamic acid 9H-fluoren-9-ylmethyl ester 848639-34-9P, 3-Methoxy-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzoic acid methyl ester 848639-35-0P, 4-[[6-[2-[2-(Piperidin-1-yl)ethoxy]phenyl]pyrimidin-4-yl]amino]benzoic acid methyl ester 848639-36-1P, 4-[[6-[2-(2-Dimethylaminoethoxy)phenyl]pyrimidin-4-yl]amino]benzoic acid methyl ester 848639-37-2P, 4-[[6-[2-(2-Diisopropylaminoethoxy)phenyl]pyrimidin-4-yl]amino]benzoic acid methyl ester 848639-38-3P, 4-[[6-[2-(2-Diethylaminoethoxy)phenyl]pyrimidin-4-yl]amino]benzoic acid methyl ester 848639-39-4P, (S,S)-4-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzoylamino]pyrrolidine-2-carboxylic acid methyl ester 848639-40-7P, (S,S)-4-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzoylamino]pyrrolidine-2-carboxylic acid 848639-41-8P, (S,S)-6-[[[4-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]benzoylamino]pyrrolidin-2-yl]carbonyl]amino]hexanoic acid 848639-42-9P, N-Cyclopentyl-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzamide 848639-43-0P, N-(4,6-Dimethylpyrimidin-2-yl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848639-44-1P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-(thiazol-2-yl)benzenesulfonamide 848639-45-2P, (1-Benzylpiperidin-3-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-46-3P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]azepan-2-one 848639-47-4P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-phenylbenzenesulfonamide 848639-48-5P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](1,2,3,4-tetrahydronaphthalen-1-yl)amine 848639-49-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](2,2,6,6-tetramethylpiperidin-4-yl)amine 848639-50-9P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-methylbenzenesulfonamide 848639-51-0P, (1,1-Dioxo-1H-benzo[b]thiophen-6-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-52-1P, N-Acetyl-4-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848639-53-2P, N-(2,6-Dimethylpyrimidin-4-yl)-4-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848639-54-3P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][4-[(piperidin-1-yl)sulfonyl]phenyl]amine 848639-55-4P, 3-[3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenoxy]piperidine-1-carboxylic acid tert-butyl ester 848639-56-5P, [6-(2-Fluoro-6-methoxyphenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848639-57-6P, [6-(4-Fluoro-2-methoxyphenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848639-58-7P, [6-(5-Fluoro-2-methoxyphenyl)pyrimidin-4-yl](3-methylsulfonylphenyl)amine 848639-59-8P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](pyridin-3-yl)amine 848639-60-1P, 2-[4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]phenyl]ethanol 848639-61-2P, (9,9-Dioxo-9,10-dihydro-9-thia-10-azaphenanthren-3-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-62-3P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](1-methyl-1H-indazol-6-yl)amine 848639-63-4P, (Benzo[1,2,5]thiadiazol-4-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-64-5P, (Benzo[1,2,5]thiadiazol-5-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-65-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][3-[(piperidin-3-yl)oxy]phenyl]amine 848639-66-7P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][1-[6-(2-

methoxyphenyl)pyrimidin-4-yl]-1H-indazol-5-ylamine 848639-67-8P, (1H-Indol-5-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-68-9P, (3-Methylsulfinylphenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-69-0P, (1H-Indazol-5-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-70-3P, 4-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]thiophene-3-carboxylic acid methyl ester 848639-71-4P, (4-Methylsulfonylbenzyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-72-5P, (5-Chloro-1H-indazol-3-yl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine 848639-73-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](5-methylisoxazol-3-yl)amine 848639-74-7P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N,N-dimethylbenzenesulfonamide 848639-75-8P, N-Ethyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848639-76-9P, 3-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-N-propylbenzenesulfonamide 848639-77-0P, [6-(2-Methoxyphenyl)pyrimidin-4-yl](2-methyl-1H-indol-5-yl)amine 848639-78-1P, N-(2-Methoxyethyl)-3-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]benzenesulfonamide 848639-79-2P, N-tert-Butyl-3-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]benzenesulfonamide 848639-80-5P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][(pyridin-2-yl)methyl]amine 848639-81-6P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][(pyridin-3-yl)methyl]amine 848639-82-7P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][(pyridin-4-yl)methyl]amine 848639-83-8P, 5-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylbenzenesulfonamide 848639-84-9P, N-(2-Methoxyethyl)-5-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]-2-methylbenzenesulfonamide 848639-85-0P, N-(2-Hydroxyethyl)-5-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]-2-methylbenzenesulfonamide 848639-86-1P, N,N-Diethyl-N'-[6-(2-methoxyphenyl)pyrimidin-4-yl]benzene-1,4-diamine 848639-87-2P, 1-(4-Chloro-3-trifluoromethylphenyl)-3-[5-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]-2-methylphenyl]urea 848639-88-3P, 1-Cyclohexyl-3-[5-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]urea 848639-89-4P, [6-(2-Methoxyphenyl)pyrimidin-4-yl][4-(pyrrolidin-1-yl)phenyl]amine 848639-90-7P, 4-Chloro-N-[6-(2-methoxyphenyl)pyrimidin-4-yl]benzene-1,3-diamine 848639-91-8P, 1-Isopropyl-3-[5-[6-(2-methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]urea 848639-92-9P, 1-[5-[6-(2-Methoxyphenyl)pyrimidin-4-ylamino]-2-methylphenyl]-3-[2-(morpholin-4-yl)ethyl]urea 848639-93-0P, 1-(2-Dimethylaminoethyl)-3-[5-[[6-(2-methoxyphenyl)pyrimidin-4-yl]amino]-2-methylphenyl]urea 848639-94-1P, (4-Chloro-3-nitrophenyl)[6-(2-methoxyphenyl)pyrimidin-4-yl]amine
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 4,6-disubstituted aminopyrimidines as modulators of protein kinases)

IT 88201-45-0 90698-26-3, p70S6K **98037-52-6, Abl kinase** 114051-78-4 137632-03-2, c-Met tyrosine kinase 137632-06-5, CSK protein kinase 141349-89-5, Src kinase 141349-91-9, Yes kinase 142243-02-5 143375-65-9, CDK1 kinase 145169-42-2, Protein kinase MAK 147014-96-8, CDK5 kinase 153190-71-7, CDK3 kinase 155215-87-5, JNK kinase 169592-62-5, CDK10 kinase 182372-13-0 260447-83-4 303014-92-8, CDK6 kinase 330197-29-0, CDK7 kinase 362517-43-9, IKKβ kinase 402476-24-8 403652-37-9, CDK8 kinase 553648-93-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; preparation of 4,6-disubstituted aminopyrimidines as modulators of protein kinases)

IT 848640-07-3P
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4,6-disubstituted aminopyrimidines as modulators of protein

kinase)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 9 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:16965 HCAPLUS Full-text
DOCUMENT NUMBER: 142:107361
TITLE: Method of blocking pathogen infection
INVENTOR(S): Pendergast, Ann Marie; Burton, Elizabeth A.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005003377	A1	20050106	US 2003-734582		20031215
PRIORITY APPLN. INFO.:			US 2002-432989P	P	20021213
			US 2003-507088P	P	20031001

AB The present invention relates, in general, to pathogens and, in particular, to a method of blocking pathogen infection and to a method of identifying agents suitable for use in such a method.
IC ICM C12Q001-68
ICS C12Q001-48
INCL 435006000; 435015000
CC 1-5 (Pharmacology)
ST antibacterial antimicrobial Abl Arg kinase **Shigella** infection
IT **Antibacterial agents**
Antimicrobial agents
Antiviral agents
Drug screening
Escherichia coli
Pathogen
Salmonella
Shigella flexneri
Signal transduction, biological
Vaccinia virus
(method of blocking pathogen infection)
IT **98037-52-6, Abl kinase** 141349-89-5, Src kinase 146838-19-9, Arg kinase 183869-11-6, Protein kinase Crk
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method of **blocking** pathogen infection)
IT 220127-57-1, STI571
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(method of blocking pathogen infection)

L66 ANSWER 10 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:927197 HCAPLUS Full-text
DOCUMENT NUMBER: 141:388648
TITLE: Novel ido (indoleamine 2,3-dioxygenase) inhibitors and methods of use
INVENTOR(S): Prendergast, George C.; Muller, Alexander J.; Duhadaway, James B.; Malachowski, William
PATENT ASSIGNEE(S): Lankenau Institute for Medical Research, USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004094409	A1	20041104	WO 2004-US5154		20040220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2520586	AA	20041104	CA 2004-2520586		20040220
EP 1606285	A1	20051221	EP 2004-713430		20040220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1795187	A	20060628	CN 2004-80008331		20040220
CN 1794986	A	20060628	CN 2004-80014321		20040220
PRIORITY APPLN. INFO.:			US 2003-458162P	P	20030327
			US 2003-527449P	P	20031205
			WO 2004-US5154	W	20040220

OTHER SOURCE(S): MARPAT 141:388648

AB Novel inhibitors of indoleamine 2,3-dioxygenase (IDO) activity are provided. In yet another embodiment of the present invention, a combination treatment protocol comprising administration of an IDO inhibitor with a signal transduction inhibitor (STI) or chemotherapeutic agent is provided, which is effective for suppressing tumor growth. In still another embodiment of the present invention, a combination treatment protocol is provided for the treatment of a chronic viral infection, comprising the administration of an IDO inhibitor and a chemotherapeutic agent.

IC ICM C07D403-06
CC 1-6 (Pharmacology)
IT Macrolides
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones; novel indoleamine dioxygenase inhibitors for treatment of tumors and viral infections and combination with chemotherapeutic agents and signal transduction inhibitors)
IT Antibodies and Immunoglobulins
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(monoclonal; novel indoleamine dioxygenase inhibitors for treatment of tumors and viral infections and combination with chemotherapeutic agents and signal transduction inhibitors)
IT Adrenal gland, neoplasm
Anti-AIDS agents
Antitumor agents
Antiviral agents
Bladder, neoplasm
Bone, neoplasm
Brain, neoplasm
Combination chemotherapy
Cytomegalovirus
Drug interactions

Esophagus, neoplasm
Head and Neck, neoplasm
Head and Neck, neoplasm
Hepatitis C virus
Human
Human coxsackievirus
Human herpesvirus 3
Human herpesvirus 4
Human immunodeficiency virus
Human papillomavirus
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Lymphoma
Mammary gland, neoplasm
Melanoma
Myoma
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Sarcoma
Skin, neoplasm
Stomach, neoplasm
Thyroid gland, neoplasm
(novel indoleamine dioxygenase inhibitors for treatment of tumors and viral infections and combination with chemotherapeutic agents and signal transduction inhibitors)

IT 79079-06-4, Epidermal growth factor receptor kinase 131384-38-8, Farnesyl transferase 137632-09-8, C-ErbB-2 protein tyrosine kinase 138238-67-2, Bcr/abl kinase 148640-14-6, Akt kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; novel indoleamine dioxygenase **inhibitors** for treatment of tumors and viral infections and combination with chemotherapeutic agents and signal transduction inhibitors)

IT 50-18-0, Cyclophosphamide 51-21-8, 5-Fluorouracil 57-22-7, Vincristine 59-05-2, Methotrexate 154-93-8, Carmustine 700-06-1, Indole 3-carbinol 865-21-4, Vinblastine 989-51-5, Epigallocatechin gallate 1327-53-3, Arsenic trioxide 1484-13-5, 9-Vinylcarbazole 1968-05-4, 3,3'-Diindolylmethane 2998-57-4, Estramustine 3030-06-6 4311-88-0 5789-24-2 6548-09-0, 5-Bromo-DL-tryptophan 15663-27-1, Cisplatin 21339-55-9, 1-Methyltryptophan 25316-40-9, Adriamycin 26988-72-7, 1-DL-Methyltryptophan 33069-62-4, Taxol 33419-42-0, Etoposide 33588-54-4 41575-94-4, Carboplatin 53123-88-9, Rapamycin 53164-05-9, Acemetacin 68712-13-0 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 100286-90-6, CPT-11 105748-59-2, Brassinin 112953-11-4 114977-28-5, Docetaxel 146426-40-6, Flavopiridol 154447-36-6, LY294002 160141-09-3, L-744832 180288-69-1, Trastuzumab 220127-57-1, STI 571 339177-26-3, ABX-EGF 786703-11-5, SSI 774
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(novel indoleamine dioxygenase inhibitors for treatment of tumors and viral infections and combination with chemotherapeutic agents and signal transduction inhibitors)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 11 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:927043 HCAPLUS Full-text

DOCUMENT NUMBER: 141:388647
TITLE: Novel methods for the treatment of cancer and viral infections
INVENTOR(S): Prendergast, George C.; Muller, Alexander J.; Duhadaway, James B.; Malachowski, William
PATENT ASSIGNEE(S): Lankenau Institute for Medical Research, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004093871	A1	20041104	WO 2004-US5155		20040220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2520172	AA	20041104	CA 2004-2520172		20040220
EP 1613308	A1	20060111	EP 2004-713378		20040220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1795187	A	20060628	CN 2004-80008331		20040220
CN 1794986	A	20060628	CN 2004-80014321		20040220
PRIORITY APPLN. INFO.:			US 2003-458162P	P	20030327
			US 2003-527449P	P	20031205
			WO 2004-US5155	W	20040220

AB Compns. and methods for the treatment of malignancy and chronic viral infection are disclosed. A method is claimed for treating a cancer comprising administering at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one signal transduction inhibitor (STI). A method is claimed for treating a cancer comprising administering at least one immunomodulator, other than IDO inhibitor, and at least one cytotoxic chemotherapeutic agent or at least one STI. A method for treating a chronic viral infection in a patient is claimed comprising administering at least one IDO inhibitor and at least one chemotherapeutic agent. Pharmaceutical compns. containing compds. of the invention for treating cancer and viral infections are also claimed.

IC ICM A61K031-405
CC 1-6 (Pharmacology)
IT Gene
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(4-Ibb ligand; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)
IT Proteins
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(B7RP1; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)
IT Glycoproteins

RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(CD40-L (antigen CD40 ligand); treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Chemokines
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(MDC (macrophage-derived chemokine); treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Chemokines
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(SLC (secondary lymphoid tissue chemokine); treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Antibodies and Immunoglobulins
CD38 (antigen)
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anti-CD38; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Antibodies and Immunoglobulins
CD40 (antigen)
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anti-CD40; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Antibodies and Immunoglobulins
Proteins
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anti-ICOS; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Antibodies and Immunoglobulins
Interleukin 10
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anti-IL-10; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Lipopolysaccharides
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(bacterial; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Macrolides
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Adrenal gland, neoplasm
Anti-AIDS agents
Antitumor agents

Antiviral agents
Bladder, neoplasm
Bone, neoplasm
Brain, neoplasm
Combination chemotherapy
Cytomegalovirus
Drug delivery systems
Drug interactions
Esophagus, neoplasm
Head and Neck, neoplasm
Head and Neck, neoplasm
Hepatitis C virus
Human
Human coxsackievirus
Human herpesvirus 3
Human herpesvirus 4
Human immunodeficiency virus
Human papillomavirus
Immunomodulators
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Lymphoma
Mammary gland, neoplasm
Melanoma
Mesothelium, neoplasm
Myoma
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Skin, neoplasm
Stomach, neoplasm
Testis, neoplasm
Thyroid gland, neoplasm
(treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Interleukin 1
Interleukin 12
Interleukin 13
Interleukin 15
Interleukin 18
Interleukin 2
Interleukin 3
Interleukin 4
Macrophage inflammatory protein 3β
Monocyte chemoattractant protein-1
Tumor necrosis factors
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT Interferons
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(α; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors,

chemotherapeutic agents, and immunomodulators)

IT Interferons
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(β; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT 9014-51-1, Indoleamine 2,3-dioxygenase 131384-38-8, Farnesyl transferase 138238-67-2, **Bcr/abl kinase** 148640-14-6, Akt kinase 150428-23-2, Cyclin-dependent protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

IT 50-18-0, Cyclophosphamide 51-21-8, 5-Fluorouracil 57-22-7, Vincristine 59-05-2, Methotrexate 154-93-8, Carmustine 244-63-3, β-Carboline 700-06-1, Indole 3-carbinol 865-21-4, Vinblastine 989-51-5, Epigallocatechin gallate 1327-53-3, Arsenic trioxide 1484-13-5, 9-Vinylcarbazole 1968-05-4, 3,3'-Diindolylmethane 2998-57-4, Estramustine 3030-06-6 4311-88-0 5789-24-2 5959-52-4, 3-Amino-2-naphthoic acid 6548-09-0, 5-Bromo-DL-tryptophan 15663-27-1, Cisplatin 21339-55-9, 1-Methyltryptophan 25316-40-9, Adriamycin 26988-72-7, 1-Methyl-DL-tryptophan 33069-62-4, Taxol 33419-42-0, Etoposide 33588-54-4 36786-90-0 41575-94-4, Carboplatin 46885-76-1, 6-Nitro-L-tryptophan 53123-88-9, Rapamycin 53164-05-9, Acemetacin 68712-13-0 72071-49-9, β-(3-Benzofuranyl)-DL-alanine 72120-71-9 74214-63-4, 3-Carboxy-β-carboline 76808-18-9 81627-83-0, Colony-stimulating factor 1 83869-56-1, GM-CSF 91985-83-0 93835-05-3 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 100286-90-6, CPT-11 105748-59-2, Brassinin 112953-11-4, UNC 01 119752-76-0, Brassilexin 125354-16-7, Docetaxal 129756-97-4 146426-40-6, Flavopiridol 154447-36-6, LY294002 159536-25-1, 5-Methylbrassinin 160141-09-3, L-744832 164299-10-9 180288-69-1, Trastuzumab 205923-56-4, C225 220127-57-1, STI 571 339177-26-3, ABX-EGF 786700-01-4 786703-11-5, SSI 774
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of cancer and viral infections using indoleamine 2,3-dioxygenase inhibitors, signal transduction inhibitors, chemotherapeutic agents, and immunomodulators)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 12 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:680002 HCAPLUS Full-text
DOCUMENT NUMBER: 141:206968
TITLE: Process for preparation of new purine derivatives, their application as drugs, pharmaceutical compositions containing them, and new uses for them
INVENTOR(S): Bordon, Pallier Florence; Haesslein, Jean Luc
PATENT ASSIGNEE(S): Aventis Pharma SA, Fr.
SOURCE: Fr. Demande, 91 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

FR 2851248	A1	20040820	FR 2003-1915	20030218
FR 2851248	B1	20050408		
AU 2004212733	A1	20040902	AU 2004-212733	20040213
CA 2515610	AA	20040902	CA 2004-2515610	20040213
WO 2004073595	A2	20040902	WO 2004-FR330	20040213
WO 2004073595	A3	20050106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1597258	A2	20051123	EP 2004-710901	20040213
BR 2004007578	A	20060214	BR 2004-7578	20040213
JP 2006517955	T2	20060803	JP 2006-502145	20040213

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:	FR 2003-1915	A	20030218
	WO 2004-FR330	A	20040213

OTHER SOURCE(S): CASREACT 141:206968; MARPAT 141:206968

AB The invention has as an aim new products I [Y = N, O, S, CHR3, :CR3; the dotted lines = single or double bond; R, R1 = H, halo, OH, alkyl, alkoxy, CN, NO2, NR4R5, CF3, CF3O, aryl, heteroaryl, S(O)nNR4R5 ; n = 0 - 2; R3 = H, halo, alkyl, CN, NO2, NR4R5, CF3, aryl; R2 = R4, OR4, SR4 or NR4R5; R4 = H, alkyl, cycloalkyl, aryl; either R4 and R5 is selected among the values of R4 or heterocyclic containing N, O and S, all optionally substituted], these products being in all the isomer forms - racemates, enantiomers or diastereomers - and pharmaceutically acceptable salts, for use as drugs. Thus, trans-N-[6-(5,6-dichloro-1H-benzimidazol-1-yl)9H- purin-2-yl]-1,4-cyclohexanediamine (II·HCl) was prepared, from 2,6-dichloropurine via amination with 5,6-dichloro-1H-benzimidazole in BuOH followed by fusion with trans-1,4-diaminocyclohexane. The protein kinase inhibitory activity of II·HCl was determined [IC50 = 1.3 μM vs CIV-CDK; 98% inhibition SRC kinase @ 20 μM; 93% inhibition CDK1 @ 20 μM; 98% inhibition ZAP kinase @ 20 μM; 93% inhibition casein kinase II @ 20 μM; 100% inhibition AKT kinase @ 20 μM; IC50 = 2 μM vs FAK kinase; IC50 = 0.84 μM vs JNK3 kinase].

IC ICM C07D473-16
ICS A61K031-52; A61P031-10; A61P035-00; A61P025-28; A61P017-06; A61P037-00

CC 26-9 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 7, 63

IT Antigens
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(autoantigens; preparation of new purine derivs. with protein kinase inhibitory activity)

IT Purine bases
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(benzimidazolyl and indolyl derivs.; preparation of new purine derivs. with protein kinase inhibitory activity)

IT Allergy inhibitors
Alzheimer's disease
Anti-Alzheimer's agents

Anti-infective agents
Anti-inflammatory agents
Antitumor agents
Cardiovascular agents
Coccidiostats
Cytotoxic agents
Fungicides
Immunomodulators
Nervous system agents
Parasiticides
Psoriasis
(preparation of new purine derivs. with protein kinase inhibitory activity)

IT 79079-06-4, EGFR tyrosine kinase 95567-89-8, CAM kinase **98037-52-6, Abl Kinase** 141349-86-2, CDK-2 141349-89-5, SRC kinase 143375-65-9, Cyclin-dependent kinase 1 144114-16-9, FAK kinase 148047-34-1, ZAP70 kinase 148640-14-6, AKT kinase 165245-99-8, Protein kinase Plk1 291756-39-3, JNK3 kinase 366806-33-9, Casein kinase II 372092-80-3, Protein kinase 443900-95-6, GSK3β
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibition**; preparation of new purine derivs. with protein kinase **inhibitory** activity)

IT 741261-29-0P
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation and N-deprotection of; preparation of new purine derivs. with protein kinase inhibitory activity)

IT 741261-07-4P 741261-08-5P 741261-11-0P 741261-13-2P 741261-14-3P 741261-22-3P 741261-23-4P 741261-25-6P 741261-26-7P 741261-27-8P 741261-31-4P 741261-34-7P 741261-35-8P 741261-38-1P 741261-40-5P 741261-48-3P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of new purine derivs. with protein kinase inhibitory activity)

IT 741261-09-6P, 6-(1H-Benzimidazol-1-yl)-9H-purin-2-amine 741261-10-9P, N,N-Dimethyl-6-(1H-benzimidazol-1-yl)-9H-purin-2-amine 741261-12-1P 741261-16-5P 741261-17-6P 741261-18-7P 741261-19-8P, N-Methyl-6-(1H-benzimidazol-1-yl)-9H-purin-2-amine 741261-20-1P, N-Cyclohexyl-6-(1H-benzimidazol-1-yl)-9H-purin-2-amine 741261-21-2P 741261-24-5P, N-Phenyl-6-(1H-benzimidazol-1-yl)-9Hpurin-2-amine 741261-28-9P 741261-30-3P 741261-47-2P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of new purine derivs. with protein kinase inhibitory activity)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 13 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:951006 HCAPLUS Full-text
DOCUMENT NUMBER: 140:16747
TITLE: Preparation of phenylpyrazines as protein kinase inhibitors for treatment of receptor type tyrosine kinase-related diseases
INVENTOR(S): Burns, Christopher John; Bu, Xianyong; Wilks, Andrew Frederick
PATENT ASSIGNEE(S): Cytopia Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099796	A1	20031204	WO 2003-AU629	20030523
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2486183	AA	20031204	CA 2003-2486183	20030523
AU 2003232919	A1	20031212	AU 2003-232919	20030523
GB 2392154	A1	20040225	GB 2003-18438	20030523
GB 2392154	B2	20050119		
EP 1513821	A1	20050316	EP 2003-727001	20030523
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1656082	A	20050817	CN 2003-811735	20030523
JP 2005535596	T2	20051124	JP 2004-507453	20030523
US 2004235862	A1	20041125	US 2003-469303	20031204
ZA 2004009341	A	20060222	ZA 2004-9341	20041119
US 2006148824	A1	20060706	US 2006-367248	20060302

PRIORITY APPLN. INFO.:	AU 2002-2515	A	20020523
	US 2002-399070P	P	20020726
	WO 2003-AU629	W	20030523
	US 2003-469303	A1	20031204

OTHER SOURCE(S): MARPAT 140:16747

AB Title compds. I [R1 = H, alkyl; Q = bond, alkyl; A = (un)substituted aryl, heteroaryl, e.g., alkyl, CH2F, CHF2, etc.; R2 = halo, alkyl, OH, etc.; Y = halo, OH, NR12R13, etc.; R12, R13 = H, CH2F, CF2H, etc.; n = 0-4; W = H, alkyl, alkenyl, etc.] and their pharmaceutically acceptable salts were prepared For example, palladium mediated coupling of chloropyrazine II, e.g., prepared from (1R)-1,2,3,4-tetrahydronaphthalen-1-amine and 2,6-dichloropyrazine, and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)phenol afforded claimed phenylpyrazine III in 47% yield. In inhibition studies of Tel-Jak2 and Tel-Jak3 cell lines, 55-examples of compds. I exhibited a capacity to inhibit 50% of cell growth at a concentration of 50 μM. Compds. I are useful for the treatment of receptor type tyrosine kinase-related diseases.

IC ICM C07D241-20
ICS C07D405-12; C07D401-12; C07D403-10; A61K031-497

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Allergy inhibitors
Angiogenesis inhibitors
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antirheumatic agents
Antitumor agents

Antiviral agents
Human
Neuromuscular blocking agents
(preparation of phenylpyrazines as protein kinase inhibitors for treatment of receptor type tyrosine kinase-related diseases)

IT 62229-50-9, EGF 98037-52-6, Abl kinase 103843-29-4, IGF-1R tyrosine kinase 137632-08-7, ERK2 kinase 141349-86-2, CDK2 kinase 141349-87-3, Fyn kinase 141349-89-5, Src kinase 141349-91-9, Yes tyrosine kinase 141460-90-4, Fes/Fps tyrosine kinase 142008-29-5, Protein kinase A 143375-65-9, CDK1 kinase 144114-16-9, Fak kinase 144247-17-6, IRR receptor tyrosine kinase 144941-32-2, Fgr kinase 147014-95-7, HER3 kinase 147014-96-8, CDK5 kinase 147014-97-9, CDK4 kinase 148047-34-1, ZAP70 kinase 148640-14-6, Protein kinase B 149147-12-6, Btk kinase 150428-23-2D, Cyclin-dependent kinase, CDK11 protein kinase 152478-56-3, JAK1 kinase 152478-57-4, JAK2 kinase 152743-99-2, HER4 kinase 153190-61-5, TYK2 kinase 153190-71-7, CDK3 kinase 155215-87-5, c-Junkinase 155948-74-6, Protein kinase FRK 157482-36-5, JAK3 kinase 165245-96-5, p38 MAPK 169592-62-5, CDK10 kinase 182938-13-2, CDK9 protein kinase 192006-95-4, Gene yrk protein kinase 303014-92-8, CDK6 kinase 330197-29-0, CDK7 kinase 403652-37-9, CDK8 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of phenylpyrazines as protein kinase inhibitors for treatment of receptor type tyrosine kinase-related diseases)

IT 629658-08-8P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(target compound; preparation of phenylpyrazines as protein kinase inhibitors
for treatment of receptor type tyrosine kinase-related diseases)

IT 629657-32-5P 629657-33-6P 629657-34-7P 629657-35-8P 629657-36-9P
629657-37-0P 629657-38-1P 629657-39-2P 629657-40-5P 629657-41-6P
629657-42-7P 629657-43-8P 629657-44-9P 629657-45-0P 629657-46-1P
629657-47-2P 629657-48-3P 629657-49-4P 629657-50-7P 629657-51-8P
629657-52-9P 629657-53-0P 629657-54-1P 629657-55-2P 629657-56-3P
629657-57-4P 629657-58-5P 629657-59-6P 629657-60-9P 629657-61-0P
629657-62-1P 629657-63-2P 629657-64-3P 629657-65-4P 629657-66-5P
629657-67-6P 629657-68-7P 629657-69-8P 629657-70-1P 629657-71-2P
629657-72-3P 629657-73-4P 629657-74-5P 629657-75-6P 629657-76-7P
629657-77-8P 629657-78-9P 629657-79-0P 629657-80-3P 629657-81-4P
629657-82-5P 629657-83-6P 629657-85-8P 629657-87-0P 629657-89-2P
629657-91-6P 629657-93-8P 629657-96-1P 629658-01-1P 629658-04-4P
629658-07-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of phenylpyrazines as protein kinase inhibitors
for treatment of receptor type tyrosine kinase-related diseases)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 14 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:892941 HCAPLUS Full-text
DOCUMENT NUMBER: 139:347736
TITLE: Method of using optical interrogation to determine a biological property of a cell or population of cells
INVENTOR(S): Schnabel, Catherine A.; Diver, Jonathan; Kariv, Ilona; Forster, Anita; Mercer, Elinore; Hall, Jeffrey; Nova,

Tina; Soohoo, William Hammel, Josh; Nguyen, Phan; Zhang, Haichuan; Tu, Eugene; Chung, Thomas D. Y.; Lykstad, Kristie Lynn; Wang, Mark M.; Butler, William Frank; Raymond, Daniel E.

PATENT ASSIGNEE(S): Genoptix, Inc., USA
SOURCE: PCT Int. Appl., 245 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 20
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093496	A1	20031113	WO 2003-US13735	20030430
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003124516	A1	20030703	US 2002-243611	20020912
US 2004009540	A1	20040115	US 2002-324926	20021219
US 2004033539	A1	20040219	US 2003-427748	20030429
AU 2003228814	A1	20031117	AU 2003-228814	20030430

PRIORITY APPLN. INFO.:

US 2002-377145P	P	20020501
US 2002-399931P	P	20020730
US 2002-400936P	P	20020801
US 2002-243611	A	20020912
US 2002-324926	A	20021219
US 2003-427748	A	20030429
US 2001-845245	A2	20010427
US 2001-993377	A2	20011114
US 2002-53507	A2	20020117
WO 2003-US13735	W	20030430

AB Optophoretic methods are used to determine one or more biol. properties or changes in biol. properties of one or more cells or cellular components. The methods use optical or photonic forces to select, identify, characterize, and/or sort whole cells or groups of cells. The methods are useful in a number of applications, including, but not limited to, drug screening applications, toxicity applications, protein expression applications, rapid clonal selection applications, biopharmaceutical monitoring and quality control applications, cell enrichment applications, viral detection, bacterial drug sensitivity screening, environmental testing, agricultural testing, food safety testing, personalized medicine applications as well as biohazard detection and anal.

IC ICM C12Q001-00
CC 9-5 (Biochemical Methods)

IT Chimeric gene, animal
Chimeric gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BCR-**ABL**, **kinase inhibitor** effect on
cells with different copy nos. of; apparatus and method for optical interrogation to determine biol. properties of cells or population of cells)

IT Saccharomyces cerevisiae

Salmonella enterica
(optical interrogation of live and dead cells of; apparatus and method for optical interrogation to determine biol. properties of cells or population of cells)
IT 138238-67-2, Bcr-Abl tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor, response of cells with different copy nos. of; apparatus and method for optical interrogation to determine biol. properties of
cells or population of cells)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 15 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:892326 HCAPLUS Full-text
DOCUMENT NUMBER: 139:377545
TITLE: Optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase positive tumor cells
INVENTOR(S): Kariv, Ilona A.; Forster, Anita; Hall, Jeffrey M.; Chung, Thomas D. y.
PATENT ASSIGNEE(S): Genoptix, Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 140 pp., Cont.-in-part of U.S. Ser. No. 243,611.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 20
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003211461	A1	20031113	US 2002-326598		20021219
US 2003124516	A1	20030703	US 2002-243611		20020912
PRIORITY APPLN. INFO.:			US 2002-377145P	P	20020501
			US 2002-399931P	P	20020730
			US 2002-400936P	P	20020801
			US 2002-243611	A2	20020912
			US 2001-845245	A2	20010427
			US 2001-993377	A2	20011114
			US 2002-53507	A2	20020117

AB A method of screening for inhibitors of the Bcr-Abl tyrosine kinase enzyme using a moving optical gradient includes the steps of providing a panel of cell lines having, on average, different copy nos. of the gene that produces the Bcr-Abl tyrosine kinase enzyme, exposing the panel of cell lines with a chemical compound, moving the cells in the panel of cell lines and the optical gradient relative to each other so as to cause displacement of at least some of the cells, measuring the displacement of at least a portion of the displaced cells in each cell line, and comparing the measured displacements with measured displacements from control cells from each cell line that have not been treated with the chemical The comparison step dets. whether the chemical compound is an inhibitor of the Bcr-Abl tyrosine kinase enzyme.
IC ICM C12Q001-00
ICS C12Q001-48
INCL 435004000; 435015000
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 1, 7
ST Bcr Abl tyrosine kinase inhibitor drug screening tumor optophoresis
IT Animal cell line

(293, optophoretic anal. study of 293 cells infection with adenovirus; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Animal cell line
(BM-3; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Animal cell line
(BV-173; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Cholecystokinin receptors
RL: ANT (Analyte); ANST (Analytical study)
(CCKA, optophoretic anal. study of CCK-1 receptor expression; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Animal cell line
(CHO, optophoretic anal. study of CCK-1 receptor expression in; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Animal cell line
(K562; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Cell activation
(T cell, optophoretic anal. of; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Animal cell line
(U937; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT T cell (lymphocyte)
(activation, optophoretic anal. of; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Adipose tissue
(adipocyte, optophoretic detection of adipogenesis; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for Bcr-Abl kinase, dosage of; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Diagnosis
(mol., optophoretic detection of cancer; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Gene dosage
(of Bcr-Abl kinase gene; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Apoptosis
(optophoretic anal. detection of; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Human adenovirus 5
(optophoretic anal. study of 293 cells infection with adenovirus; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine **kinase** pos. tumor cells)

IT Drug resistance
(optophoretic anal. study of; optophoretic screening of drugs exhibiting **inhibitory** effect on Bcr-**Abl** tyrosine

kinase pos. tumor cells)
IT Optical instruments
(optophoretic apparatus; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Antitumor agents
Bioassay
Drug screening
Human
Neoplasm
Optical traps
(optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Cell cycle
(optophoretic study of cells in different cell cycle stages; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Salmonella enterica
Staphylococcus aureus
(optophoretic study of live and dead microbes; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Saccharomyces cerevisiae
(optophoretic study of wild type/mutant yeast strains; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Separation
(optophoretic, of cells; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Secretion (process)
(protein, optophoretic anal. study of GM-CSF secretion; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Infection
(viral, optophoretic anal. study of 293 cells infection with adenovirus; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT Animal cell line
(with different copy nos. of Bcr-Abl gene; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT 83869-56-1, GM-CSF
RL: ANT (Analyte); ANST (Analytical study)
(optophoretic anal. study of GM-CSF secretion; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT 114-07-8, Erythromycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(optophoretic determination of resistance to; optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)
IT 138238-67-2, Bcr-Abl tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(optophoretic screening of drugs exhibiting inhibitory effect on Bcr-Abl tyrosine kinase pos. tumor cells)

L66 ANSWER 16 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:51[illegible] HCAPLUS Full text
DOCUMENT NUMBER: 139:65742
TITLE: Method of using optical interrogation to determine a biological property of a cell or population of cells
INVENTOR(S): Chung, Thomas D. Y.; Forster, Anita; Hall, Jeff; Kariv, Ilona; Lykstad, Kris; Schnabel, Catherine A.; Soo, Hoo William; Diver, Jonathan
PATENT ASSIGNEE(S): Genoptix, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 71 pp., Cont.-in-part of U.S. Ser. No. 53,507.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 20
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003124516	A1	20030703	US 2002-243611	20020912
US 2003007894	A1	20030109	US 2001-845245	20010427
US 2002115164	A1	20020822	US 2001-993377	20011114
US 6784420	B2	20040831		
US 2002160470	A1	20021031	US 2002-53507	20020117
US 2003194755	A1	20031016	US 2002-326796	20021219
US 2003211461	A1	20031113	US 2002-326598	20021219
US 2004009540	A1	20040115	US 2002-324926	20021219
US 2004023310	A1	20040205	US 2002-326568	20021219
US 2004053209	A1	20040318	US 2002-326885	20021219
US 2004033539	A1	20040219	US 2003-427748	20030429
WO 2003093496	A1	20031113	WO 2003-US13735	20030430
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003228814	A1	20031117	AU 2003-228814	20030430

PRIORITY APPLN. INFO.:		
US 2001-845245	A2	20010427
US 2001-993377	A2	20011114
US 2002-53507	A2	20020117
US 2000-248451P	P	20001113
US 2002-377145P	P	20020501
US 2002-399931P	P	20020730
US 2002-400936P	P	20020801
US 2002-243611	A2	20020912
US 2002-324926	A2	20021219
US 2003-427748	A	20030429
WO 2003-US13735	W	20030430

AB Optophoretic methods are used to determine one or more biol. properties or changes in biol. properties of one or more cells or cellular components. The methods use optical or photonic forces to select, identify, characterize, and/or sort whole cells or groups of cells. The methods are useful in a number of applications, including, but not limited to, drug screening applications, toxicity applications, protein expression applications, rapid clonal selection applications, biopharmaceutical monitoring and quality control applications, cell enrichment applications, viral detection, bacterial

drug sensitivity screening, environmental testing, agricultural testing, food safety testing, as well as biohazard detection and anal. A whole blood sample was stained for 15 min with New Methylene Blue, a nucleic acid stain that differentially stains the nucleated white blood cells vs. the unnucleated red blood cells. The sample was diluted in PBS and mounted on a fluorosilane coated slide. A Michelson interferometer and a 150 mW, 812 nm laser system was used to generate optical gradient fields. The fringe period was adjusted to 15 μm and was moved at 22 μm/s. The white blood cells were moved by the fringes while the red blood cells were not.

IC ICM C12Q001-70
ICS G01N033-53; G01N033-567
INCL 435005000; 435007200
CC 9-5 (Biochemical Methods)
IT Chimeric gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BCR-**ABL**, **kinase inhibitor** effect on cells with different copy nos. of; apparatus and method for optical interrogation to determine biol. properties of cells or population of cells)
IT Saccharomyces cerevisiae
Salmonella enterica
(optical interrogation of live and dead cells of; apparatus and method for optical interrogation to determine biol. properties of cells or population of cells)
IT 138238-67-2, Bcr-**Abl** tyrosine **kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**, response of cells with different copy nos. of; apparatus and method for optical interrogation to determine biol. properties of cells or population of cells)

L66 ANSWER 17 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:906175 HCAPLUS Full-text
DOCUMENT NUMBER: 138:14074
TITLE: Preparation of benzo[g]quinoxalines for use against infectious diseases
INVENTOR(S): Pato, Janos; Keri, Gyoergy; Oerfi, Laszlo; Waczek, Frigyes; Horvath, Zoltan; Banhegyi, Peter; Szabadkai, Istvan; Marosfalvi, Jenoe; Hegymegi-barakonyi, Balint; Szekelyhidi, Zsolt; Greff, Zoltan; Choidas, Axel; Bacher, Gerald; Daub, Henrik; Obert, Sabine; Kurtenbach, Alexander; Habenberger, Peter
PATENT ASSIGNEE(S): Axxima Pharmaceuticals Ag, Germany; et al.
SOURCE: PCT Int. Appl., 237 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094796	A2	20021128	WO 2002-EP5573	20020521
WO 2002094796	A3	20031204		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002312927	A1	20021203	AU 2002-312927		20020521
US 2004171603	A1	20040902	US 2003-715591		20031118
PRIORITY APPLN. INFO.:			EP 2001-112289	A	20010518
			US 2001-292325P	P	20010522
			US 2001-298902P	P	20010619
			EP 2001-115508	A	20010627
			EP 2002-7923	A	20020409
			WO 2002-EP5573	W	20020521
			WO 2003-EP3697	A2	20030409

OTHER SOURCE(S): MARPAT 138:14074

AB The present invention relates to benzo[g]quinoxaline derivs. (shown as I; e.g. 2,3-bis(2-thienyl)benzo[g]quinoxaline and benzo[g]quinoxalin-2-yl(3-bromophenyl)amine), processes for manufacturing said benzo[g]quinoxaline derivs., the use of the benzo[g]quinoxaline derivs. as pharmaceutically active agents, especially for the prophylaxis and/or treatment of infectious diseases and opportunistic infections, diabetes, cancer, inflammation, as well as compns. containing at least one benzo[g]quinoxaline derivative and/or pharmaceutically acceptable salt thereof. Further, the present invention is directed to methods for preventing and/or treating of infectious diseases, diabetes, cancer, and inflammation using the inventive benzo[g]quinoxaline derivs. The inventive benzo[g]quinoxaline derivs. exert their antiproliferative effect on M. bovis BCG and M. tuberculosis Erdmann at concns. between <<1 μM and 32 μM. In contrast, growth of E. coli XI-1 blue was not affected by benzo[g]quinoxaline derivs. at concns. >10 μM. The benzo[g]quinoxaline compds. are able to inhibit HI virus replication up to 63% after 6 days at a concentration of 1 μM. 5,10-Dibromo-2-(thiophen-3-yl)-3-(thiophen-2-yl)benzo[g]quinoxaline is able to decrease the activity of the herpes viral target UL-97 by 75%. Results for inhibition of HCMV target RICK for 5 I, of influenza replication for 7 I, of hepatitis B virus for 5 I, of TNFα signaling for 11 I, of human cellular protein kinases (Akt, Abl, PDGFR, Src) for 7 I, of A549 and Jurkat cells for 18 I, of human cellular protein kinase Akt known as a target for diabetes for 4 I, and of human protein kinases SRPK1 and SRPK2 (indicative of hepatitis B virus replication inhibition) for 8 and 1 I, resp., are tabulated. Results for activation of the insulin receptor InsR by 3 I, effect of 2 I on viability of Huh-5-2 replicon cells by the Alamar Blue toxicity assay, effect of 2 I on autonomous replication of hepatitis C virus replicons in the Huh-5-2 cell line by luciferase reporter assay, are tabulated. In I: R1 and R2 = -(CH2)p-NH-(CH2)n-R9, -(CH2)s-S-(CH2)m-R10, -(CH2)m-O-(CH2)p-R11, -(CH2)r-R3, -CH:CH-R11, -(CH2)m-CH(OH)(CH2)p-R11, -(CH2)q-R11, -R9, R10, -R12, -R13, etc. R3, R4, R5, R6, R7, and R8 = -H, -F, -Cl, -Br, -I, -SO3H, -SO3NH2, -(CH2)s-COOR16, -(CH2)p-COOR17, -OR16, -SR16, -NR16R17, -OOCR16, -OOCR17, -NH-CO-R16, -NH-CO-R17, -CO-NH-R16, -CO-NH-R17, -NO2, -N3, -CN, -OCN, -NCO, -SCN, -NCS, CO-R16, CO-R17, -COCN, -CONR16R17, -SOR16, -SO2R16, -SO2R17, -SO3R16, -SO3R17, OCF3. R9, R10, and R11 = -CN, NR16R17, -NHR16, NHR17, etc. R12, R13, R14, and R15 = R3, R4, R5, R6, R16, R17, CH(CO2R16)(CO2R17), CH(CN)(CO2R16), CH(CN)C(O)NHAr (Ar = R14- and R15-substituted phenyl); R16 and R17 = -H, -CH3, -C2H5, -Pr, -CHMe2, -Bu, -C5H11, -C6H13, -cyclo-C6H11, -cyclo-C5H9, -cyclo-C4H7, -cyclo-C3H5, -(CH2)r-CHMe2, -CHMeEt, -CMe3, -CH:CH2, -CH2-CH:CH2, Ph, --CH2Ph, -C2H4Ph, -CH(CN)2, -CF3, -CCl3, -CBr3, -C2F5, -(CH2)r-OH, -CH2F, -CH2Cl, -CH2Br, -CH2I, -CHF2, -CHCl2, -CHBr2, -(CH2)r-SH, -C6H4-CH3, -C6H3Me2, pyridyl, 2-pyrimidinyl, etc. M = 0-6, n = 0-6, p = 0-6, q = 0-6, r = 1-6, s = 0-6. Also claimed are the corresponding N-oxides in position 1 and/or 4 of these compds., the corresponding reduced forms of these compds. wherein the double bond in position 1 and/or 3 is hydrogenated, and pharmaceutically acceptable

benzo salts of I. About 42 example preps. and 406 compds. with characterization data are included. 1H-benzo[g]quinoxaline-2-one was prepared in 90% yield by dissolving 20 mmol 2,3-diaminonaphthalene in a mixture of 5 mL DMF and 50 mL EtOH and adding 5 mL aqueous solution (50%) of glyoxalic acid and the mixture was stirred for 2 h at reflux temperature The reaction mixture was cooled to room temperature and the product was filtered, washed two times with Et2O and dried.

IC ICM C07D241-00

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Antibodies and Immunoglobulins
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(HBV; combined with benzo[g]quinoxalines for use against infectious diseases)

IT Ribozymes
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hammerhead; combined with benzo[g]quinoxalines for use against infectious diseases)

IT Antibodies and Immunoglobulins
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(monoclonal, directed against HBV; combined with benzo[g]quinoxalines for use against infectious diseases)

IT Adenoviridae
Anti-AIDS agents
Antibacterial agents
Antidiabetic agents
Antitumor agents
Antiviral agents
Bladder, neoplasm
Bovine immunodeficiency virus
Bovine leukemia virus
Caprine arthritis encephalitis virus
Carcinoma
Central nervous system, neoplasm
Equine infectious anemia virus
Feline immunodeficiency virus
Ground squirrel hepatitis B virus
Head and Neck, neoplasm
Head and Neck, neoplasm
Hepadnaviridae
Hepatitis B virus
Hepatitis C virus
Herpesviridae
Human
Human T-lymphotropic virus 1
Human T-lymphotropic virus 2
Human herpesvirus 1
Human herpesvirus 2
Human herpesvirus 3
Human herpesvirus 4
Human herpesvirus 5
Human herpesvirus 8
Human immunodeficiency virus 1
Human immunodeficiency virus 2
Human respiratory syncytial virus
Influenza
Kidney, neoplasm
Lentivirus
Leprosy
Leukemia

Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Melanoma
Neoplasm
Ovary, neoplasm
Paramyxovirus
Prostate gland, neoplasm
Psoriasis
Retroviridae
Simian immunodeficiency virus
Stomach, neoplasm
Testis, neoplasm
Tuberculosis
Tuberculostatics
Visna-Maedi virus
Woodchuck hepatitis virus
(preparation of benzo[g]quinoxalines for use against infectious diseases)

IT Interferons
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(α; combined with benzo[g]quinoxalines for use against infectious diseases)

IT 3424-98-4, Epavudine 29984-33-6D, Ara-AMP, prodrugs 39809-25-1, Penciclovir 40093-94-5, Epcitabine 62304-98-7, Zadaxin 69521-94-4, Thymosin α-1 81117-35-3, N-Nonyldeoxynojirimycin 98530-12-2, Intron A 120443-30-3, (-)-Carbovir 127759-89-1, Lobucavir 134678-17-4, Lamivudine 142217-69-4, Entecavir 142340-99-6, Adefovir dipivoxil 143491-54-7, Racivir 143491-57-0, Coviracil 145514-01-8, DXG 145514-04-1, DAPD 147127-20-6, Tenofovir 163252-36-6, Clevudine 165456-81-5, Combivir 194918-86-0, HDP-P-acyclovir 364057-50-1, Trizivir 386212-08-4, Genevax 386212-09-5, Hepagene
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combined with benzo[g]quinoxalines for use against infectious diseases)

IT 19187-03-2P, 2,3-Dichlorobenzo[g]quinoxaline 95379-91-2P, 2,3-Bis(bromomethyl)benzo[g]quinoxaline 438574-47-1P, 2,3-Bis(4-fluorophenyl)benzo[g]quinoxaline 476635-78-6P, 2-Chlorobenzo[g]quinoxaline 476635-79-7P, 2-(2-Thienyl)-3-chlorobenzo[g]quinoxaline 476636-02-9P, 2-Methyl-3-(thiophen-2-yl)-1,2-dihydrobenzo[g]quinoxaline 476636-03-0P, 2-Methyl-3-(thiophen-2-yl)benzo[g]quinoxaline 476636-45-0P 476636-46-1P, 2-(3-Chlorobenzo[g]quinoxalin-2-yl)malonic acid diethyl ester 476636-67-6P, 2-(3,4-Dimethoxyphenylamino)benzo[g]quinoxaline 476637-16-8P 476637-17-9P 476637-97-5P, (3-Chlorobenzo[g]quinoxalin-2-yl)(3-chlorophenyl)amine 476637-98-6P, (3-Chlorobenzo[g]quinoxalin-2-yl)(4-trifluoromethylphenyl)amine 476638-14-9P, 4-[(3-Chlorobenzo[g]quinoxalin-2-yl)sulfanyl]phenylamine 476639-26-6P, 2,3-Bis(thiophen-2-yl)benzo[g]quinoxaline-6-sulfonic acid sodium salt
RL: **PAC (Pharmacological activity)**; RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of benzo[g]quinoxalines for use against infectious diseases)

IT 857-48-7P, 2,3-Bis(pyrid-2-yl)benzo[g]quinoxaline 36305-72-3P, 2,3-Diphenylbenzo[g]quinoxaline 52736-74-0P, 2,3-Dimethylbenzo[g]quinoxaline 66367-18-8P, 3,4-Dihydro-1H-benzo[g]quinoxalin-2-one 94370-19-1P, 2,3-Di-p-tolylbenzo[g]quinoxaline 168835-98-1P, 2-Phenylbenzo[g]quinoxaline 476635-87-7P, 2,3-Bis(2-thienyl)benzo[g]quinoxaline 476635-88-8P, 2-p-Tolylbenzo[g]quinoxaline 476635-89-9P, 2-(3-

Chlorophenyl)benzo[g]quinoxaline 476635-90-2P, 2-(4-Chlorophenyl)benzo[g]quinoxaline 476635-91-3P, 2-(4-Bromophenyl)benzo[g]quinoxaline 476635-92-4P, 2-(Adamantan-2-yl)benzo[g]quinoxaline 476635-93-5P, 2,3-Bis(5-bromo-2-hydroxyphenyl)benzo[g]quinoxaline 476635-94-6P, 2,3-Bis(3-methoxyphenyl)benzo[g]quinoxaline 476635-95-7P, 2,3-Bis(furan-2-yl)benzo[g]quinoxaline 476635-96-8P, 2-(Thiophen-3-yl)-3-(thiophen-2-yl)benzo[g]quinoxaline 476635-97-9P, 2,3-Bis(thiophen-3-yl)benzo[g]quinoxaline 476635-98-0P, 2,3-Dihydro-1H-benzo[g]cyclopenta[b]quinoxaline-1,3-dicarboxylic acid diethyl ester 476635-99-1P, 2-(3,4-Dimethoxyphenyl)benzo[g]quinoxaline 476636-00-7P, 2-(3,4-Dihydroxyphenyl)benzo[g]quinoxaline 476636-04-1P, [5-[3-(4-Methoxycarbonylmethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid methyl ester 476636-05-2P, [5-[3-(5-Methoxycarbonylmethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid methyl ester 476636-06-3P, 2,3-Bis(2-methoxycarbonylethylthiophen-5-yl)benzo[g]quinoxaline 476636-07-4P, 2,3-Bis(2-ethoxycarbonylpropylthiophen-5-yl)benzo[g]quinoxaline 476636-08-5P, [5-[3-(4-Carboxymethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-3-yl]acetic acid 476636-09-6P, 2,3-Bis(2-carboxymethylthiophen-5-yl)benzo[g]quinoxaline 476636-10-9P, 2,3-Bis(2-carboxypropylthiophen-5-yl)benzo[g]quinoxaline 476636-11-0P, 2,3-Bis(2-carboxyethylthiophen-5-yl)benzo[g]quinoxaline 476636-12-1P, [5-[5,10-Dibromo-3-(4-carboxymethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-3-yl]acetic acid 476636-13-2P, [5-[5,10-Dibromo-3-(5-carboxymethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid 476636-14-3P 476636-15-4P 476636-16-5P 476636-17-6P 476636-18-7P 476636-19-8P 476636-20-1P 476636-21-2P 476636-22-3P 476636-23-4P 476636-24-5P, 2,3-Bis[(phenylsulfanyl)methyl]benzo[g]quinoxaline 476636-25-6P, 2,3-Bis[(4-methylphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-26-7P, 2,3-Bis[(2-methoxyphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-27-8P, 2,3-Bis[(4-methoxyphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-28-9P, 2,3-Bis[(2,5-dichlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-29-0P, 2,3-Bis[(2,6-dichlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-30-3P, 2,3-Bis[(3,4-dichlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-31-4P, 2,3-Bis[(2,4-dimethylphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-32-5P, 2,3-Bis[(2,5-dimethylphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-33-6P, 2,3-Bis[(2,3,5,6-tetrafluorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-34-7P, 2,3-Bis[(2-chlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-35-8P, 2,3-Bis[(3-chlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-36-9P, 2,3-Bis[(4-chlorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-37-0P, 2,3-Bis[(2-bromophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-38-1P, 2,3-Bis[(3-bromophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-39-2P, 2,3-Bis[(4-fluorophenylsulfanyl)methyl]benzo[g]quinoxaline 476636-40-5P, 2,3-Bis[(2-methylphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-41-6P, 2,3-Bis[(3-methylphenylsulfanyl)methyl]benzo[g]quinoxaline 476636-42-7P, 2,3-Bis[[(4,5-dihydrothiazol-2-yl)sulfanyl]methyl]benzo[g]quinoxaline 476636-43-8P, 2,3-Bis[[(1H-benzimidazol-2-yl)sulfanyl]methyl]benzo[g]quinoxaline 476636-44-9P 476636-47-2P 476636-48-3P 476636-49-4P 476636-50-7P, (Benzo[g]quinoxalin-2-yl)(2-ethoxycarbonylphenyl)amine 476636-51-8P, 4-(Benzo[g]quinoxalin-2-ylamino)benzenesulfonamide 476636-52-9P, (Benzo[g]quinoxalin-2-yl)(3,4-dimethylphenyl)amine 476636-53-0P, (Benzo[g]quinoxalin-2-yl)[3,5-bis(ethoxycarbonyl)phenyl]amine 476636-54-1P, (Benzo[g]quinoxalin-2-yl)(2-hydroxy-4-methylphenyl)amine 476636-55-2P, (Benzo[g]quinoxaline-2-yl)(phenyl)amine 476636-56-3P, (Benzo[g]quinoxalin-2-yl)(biphenyl-4-yl)amine 476636-57-4P, (Benzo[g]quinoxalin-2-yl)(4-methylphenyl)amine 476636-58-5P, (Benzo[g]quinoxalin-2-yl)(4-phenoxyphenyl)amine 476636-59-6P,

(Benzo[g]quinoxalin-2-yl)(4-bromophenyl)amine 476636-60-9P,
(Benzo[g]quinoxalin-2-yl)(4-methylsulfanylphenyl)amine 476636-61-0P,
[4-(Benzo[g]quinoxalin-2-ylamino)phenyl](phenyl)methanone 476636-62-1P,
(Benzo[g]quinoxalin-2-yl)(2,4-dimethoxyphenyl)amine 476636-63-2P,
(Benzo[g]quinoxalin-2-yl)(2-hydroxy-5-chlorophenyl)amine 476636-64-3P,
(Benzo[g]quinoxalin-2-yl)(3-fluoro-4-methylphenyl)amine 476636-65-4P,
(Benzo[g]quinoxalin-2-yl)[2-(2-chlorophenyl)ethyl]amine 476636-66-5P,
(Benzo[g]quinoxalin-2-yl)(3-bromophenyl)amine 476636-68-7P,
4-(Benzo[g]quinoxaline-2-ylamino)benzene-1,2-diol 476636-69-8P,
N-(Benzo[g]quinoxalin-2-yl)-N'-(4-fluorophenyl)hydrazine 476636-70-1P,
N-(Benzo[g]quinoxalin-2-yl)-N'-(2,4-dichlorophenyl)hydrazine
476636-71-2P, N-(Benzo[g]quinoxalin-2-yl)-N'-(3-chlorophenyl)hydrazine
476636-72-3P, N-(Benzo[g]quinoxalin-2-yl)-N'-(4-chlorophenyl)hydrazine
476636-73-4P, 1-(2-Nitrophenyl)-2-(3-(thiophen-2-yl)benzo[g]quinoxaline-2-yl)ethanol 476636-74-5P, (Benzo[g]quinoxalin-2-yl)(4-ethylphenyl)amine
476636-75-6P, N-[4-(Benzo[g]quinoxalin-2-ylamino)phenyl]acetamide
476636-76-7P, (Benzo[g]quinoxalin-2-yl)(3-chlorophenyl)amine
476636-77-8P, (Benzo[g]quinoxalin-2-yl)(4-chlorophenyl)amine
476636-78-9P, (Benzo[g]quinoxalin-2-yl)(3-fluorophenyl)amine
476636-79-0P, (Benzo[g]quinoxalin-2-yl)(2-fluorophenyl)amine
476636-80-3P, (Benzo[g]quinoxalin-2-yl)(2,4-dichlorophenyl)amine
476636-81-4P, (Benzo[g]quinoxalin-2-yl)(4-hydroxyphenyl)amine
476636-82-5P, (Benzo[g]quinoxalin-2-yl)(3-iodophenyl)amine 476636-83-6P,
(Benzo[g]quinoxalin-2-yl)(3,4-dichlorophenyl)amine 476636-84-7P,
(Benzo[g]quinoxalin-2-yl)(3-trifluoromethylphenyl)amine 476636-85-8P,
(Benzo[g]quinoxalin-2-yl)(4-trifluoromethylphenyl)amine 476636-86-9P,
(5-Chloro-2-methylphenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine
476636-87-0P, (2-Fluorophenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine 476636-88-1P, (4-Trifluoromethylphenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476636-89-2P, (3,4-Dimethoxyphenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476636-90-5P,
(2,5-Dimethoxyphenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine
476636-91-6P, (4-Chlorophenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476636-92-7P, (3-Fluorophenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476636-93-8P, (3-Hydroxyphenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine 476636-94-9P,
N-[4-[[3-(Thiophen-2-yl)benzo[g]quinoxalin-2-yl]amino]phenyl]acetamide
476636-95-0P, (2-Hydroxy-4-methylphenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine 476636-96-1P, (3-Chlorophenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine 476636-97-2P,
(4-Bromophenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine
476636-98-3P, (3-Trifluoromethylphenyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476636-99-4P, (2-(Morpholin-4-yl)ethyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476637-00-0P,
[3-(4-Methylpiperazin-1-yl)propyl](3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476637-01-1P, (2-(Piperidin-1-yl)ethyl)(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)amine 476637-02-2P, N-(3-Bromophenyl)-N'-(3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl)hydrazine 476637-03-3P,
(4-Butylphenyl)[3-(thiophen-2-yl)benzo[g]quinoxalin-2-yl]amine
476637-08-8P, (Benzo[g]quinoxalin-2-yl)[2-(2-bromophenyl)-5-tert-butyl-2H-pyrazol-3-yl]amine 476637-09-9P, (Benzo[g]quinoxalin-2-yl)[5-tert-butyl-2-(3-nitrophenyl)-2H-pyrazol-3-yl]amine 476637-10-2P,
(Benzo[g]quinoxalin-2-yl)[2-(3-fluorophenyl)-5-tert-butyl-2H-pyrazol-3-yl]amine 476637-11-3P, (Benzo[g]quinoxalin-2-yl)[2-(3-trifluoromethylphenyl)-5-tert-butyl-2H-pyrazol-3-yl]amine 476637-12-4P,
(Benzo[g]quinoxalin-2-yl)[2-(2-methylphenyl)-5-tert-butyl-2H-pyrazol-3-yl]amine 476637-13-5P, (Benzo[g]quinoxalin-2-yl)[5-tert-butyl-2-(4-nitrophenyl)-2H-pyrazol-3-yl]amine 476637-14-6P 476637-15-7P
476637-18-0P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-(3-(imidazol-1-yl)propyl)benzo[g]quinoxaline-2,3-diamine 476637-19-1P,

2-[[3-[[5-tert-Butyl-2-(3-nitrophenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl]amino]ethanol 476637-20-4P, 2-[[3-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl]amino]ethanol 476637-21-5P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(3-methylbutyl)benzo[g]quinoxaline-2,3-diamine 476637-22-6P, 3-[[3-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl]amino]propanol 476637-23-7P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-[2-(3-fluorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-24-8P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-[2-(3-chlorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-25-9P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-[2-(4-methoxyphenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-26-0P, 3-[[3-[[5-tert-Butyl-2-(4-methoxyphenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl]amino]propanol 476637-27-1P, 3-[[3-[(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)amino]benzo[g]quinoxalin-2-yl]amino]propanol 476637-28-2P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-[2-(2-chlorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-29-3P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-[2-(4-methoxyphenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-30-6P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-(5-methylfuran-2-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-31-7P, 2-[[3-[[5-tert-Butyl-2-(4-methoxyphenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl]amino]ethanol 476637-32-8P, N-[5-tert-Butyl-2-(4-methoxyphenyl)-2H-pyrazol-3-yl]-N'-(3-methylbutyl)benzo[g]quinoxaline-2,3-diamine 476637-33-9P, N-[5-tert-Butyl-2-(4-methoxyphenyl)-2H-pyrazol-3-yl]-N'-(3-(imidazol-1-yl)propyl)benzo[g]quinoxaline-2,3-diamine 476637-34-0P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-[2-(2-chlorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-35-1P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(2-cyclohex-1-enylethyl)benzo[g]quinoxaline-2,3-diamine 476637-36-2P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(pyridin-3-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-37-3P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(5-methylfuran-2-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-38-4P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(3-(imidazol-1-yl)propyl)benzo[g]quinoxaline-2,3-diamine 476637-39-5P, 2-[[3-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]amino]benzo[g]quinoxalin-2-yl](2-hydroxyethyl)amino]ethanol 476637-40-8P, N-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-N'-(pyridin-4-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-41-9P, N-(1-Benzylpiperidin-4-ylmethyl)-N'-[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]benzo[g]quinoxaline-2,3-diamine 476637-42-0P, 2-[[3-[(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)amino]benzo[g]quinoxalin-2-yl]amino]ethanol 476637-43-1P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-(3-methylbutyl)benzo[g]quinoxaline-2,3-diamine 476637-44-2P, N-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-N'-(2-cyclohex-1-enylethyl)benzo[g]quinoxaline-2,3-diamine 476637-45-3P, N,N'-Bis(pyridin-3-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-46-4P, N,N'-Diphenylbenzo[g]quinoxaline-2,3-diamine 476637-47-5P 476637-48-6P, N,N'-Bis(4-chlorophenyl)benzo[g]quinoxaline-2,3-diamine 476637-49-7P, N,N'-Bis(4-bromophenyl)benzo[g]quinoxaline-2,3-diamine 476637-50-0P, N,N'-Bis(4-phenoxyphenyl)benzo[g]quinoxaline-2,3-diamine 476637-51-1P, N,N'-Bis(3,4-dimethylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-52-2P, N,N'-Bis(4-methylsulfanylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-53-3P, N,N'-Bis(3-methoxyphenyl)benzo[g]quinoxaline-2,3-diamine 476637-54-4P, N,N'-Bis(3-chloro-4-methylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-55-5P, N,N'-Bis(3-bromophenyl)benzo[g]quinoxaline-

2,3-diamine 476637-56-6P, N,N'-Bis(3-fluorophenyl)benzo[g]quinoxaline-2,3-diamine 476637-57-7P, N,N'-Bis(3-methylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-58-8P, N,N'-Bis(3-chlorophenyl)benzo[g]quinoxaline-2,3-diamine 476637-59-9P, N,N'-Bis(4-ethylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-60-2P, N,N'-Bis(4-butylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-61-3P, N,N'-Bis(3-trifluoromethylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-62-4P, N,N'-Bis(3,4-dimethoxyphenyl)benzo[g]quinoxaline-2,3-diamine 476637-63-5P, N,N'-Bis(3-fluoro-4-methylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-64-6P, N,N'-Bis(4-methylphenyl)benzo[g]quinoxaline-2,3-diamine 476637-65-7P, N,N'-Bis(2,5-dimethoxyphenyl)benzo[g]quinoxaline-2,3-diamine 476637-66-8P, N-[4-[[3-[(4-Acetylaminophenyl)amino]benzo[g]quinoxalin-2-yl]amino]phenyl]acetamide 476637-67-9P, N,N'-Bis(3-methylbutyl)benzo[g]quinoxaline-2,3-diamine 476637-68-0P, N,N'-Bis(2-hydroxyethyl)benzo[g]quinoxaline-2,3-diamine 476637-69-1P, N,N'-Bis(5-methylfuran-2-ylmethyl)benzo[g]quinoxaline-2,3-diamine 476637-70-4P, N,N'-Bis[2-(3-fluorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-71-5P, N,N'-Bis[2-(3-chlorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-72-6P, N,N'-Bis(pyridin-4-yl)benzo[g]quinoxaline-2,3-diamine 476637-73-7P, N,N'-Bis[2-(4-methoxyphenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-74-8P, N,N'-Bis[2-(2-chlorophenyl)ethyl]benzo[g]quinoxaline-2,3-diamine 476637-75-9P, N,N'-Bis(2-cyclohex-1-enylethyl)benzo[g]quinoxaline-2,3-diamine 476637-76-0P, N,N'-Bis(1-benzylpiperidin-4-yl)benzo[g]quinoxaline-2,3-diamine 476637-77-1P, N,N'-Bis[3-(imidazol-1-yl)propyl]benzo[g]quinoxaline-2,3-diamine 476637-78-2P, N,N'-Bis(3-hydroxypropyl)benzo[g]quinoxaline-2,3-diamine 476637-79-3P, 2-(Piperidin-1-yl)benzo[g]quinoxaline 476637-80-6P, 1-Benzo[g]quinoxalin-2-ylpiperidine-4-carboxylic acid ethyl ester 476637-81-7P, 2-(Morpholin-4-yl)benzo[g]quinoxaline 476637-82-8P, 2-(4-Methylpiperazin-1-yl)benzo[g]quinoxaline 476637-83-9P, 4-Benzo[g]quinoxalin-2-ylpiperazine-1-carboxylic acid ethyl ester 476637-84-0P, 2-(4-Phenylpiperazin-1-yl)benzo[g]quinoxaline 476637-85-1P, 2-(Morpholin-4-yl)-3-(thiophen-2-yl)benzo[g]quinoxaline 476637-86-2P, 1-(3-(Thiophen-2-yl)benzo[g]quinoxalin-2-yl)piperidine-4-carboxylic acid ethyl ester 476637-87-3P, 2-[4-(4-Fluorophenyl)piperazin-1-yl]benzo[g]quinoxaline 476637-88-4P, 2-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]benzo[g]quinoxaline 476637-89-5P, 2-[4-(2-Methoxyphenyl)piperazin-1-yl]benzo[g]quinoxaline 476637-90-8P, 2-(4-(Pyridin-2-yl)piperazin-1-yl)benzo[g]quinoxaline 476637-91-9P, 2-(4-(Pyrimidin-2-yl)piperazin-1-yl)benzo[g]quinoxaline 476637-92-0P, 2-[4-(2-Fluorophenyl)piperazin-1-yl]benzo[g]quinoxaline 476637-93-1P 476637-94-2P 476637-95-3P, (4-Bromophenyl)(3-chlorobenzo[g]quinoxalin-2-yl)amine 476637-96-4P, (3-Chlorobenzo[g]quinoxalin-2-yl)(3-fluorophenyl)amine 476637-99-7P, 2-(4-Chlorophenoxy)benzo[g]quinoxaline 476638-00-3P, 2-(4-Bromophenoxy)benzo[g]quinoxaline 476638-01-4P, 2-(3-Methoxyphenoxy)benzo[g]quinoxaline 476638-02-5P, 2-(4-Methoxyphenoxy)benzo[g]quinoxaline 476638-03-6P, 2-(3,5-Dimethoxyphenoxy)benzo[g]quinoxaline 476638-04-7P, 2-(4-Bromophenoxy)-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-05-8P, 2-(4-Chlorophenoxy)-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-06-9P, 2-(3,5-Dimethoxyphenoxy)-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-07-0P, 2-(2,5-Dichlorophenylsulfanyl)benzo[g]quinoxaline 476638-08-1P, 2-[(1H-Imidazol-2-yl)sulfanyl]benzo[g]quinoxaline 476638-09-2P, 2-[(1H-[1,2,4]Triazol-3-yl)sulfanyl]benzo[g]quinoxaline 476638-10-5P, 2-(Pyrimidin-2-ylsulfanyl)-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-11-6P, 2-[(1H-Imidazol-2-yl)sulfanyl]-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-12-7P, 2-(2,5-Dichlorophenylsulfanyl)-3-(thiophen-2-yl)benzo[g]quinoxaline 476638-13-8P, 2-(Pyrimidin-2-ylsulfanyl)benzo[g]quinoxaline

476638-15-0P, [5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl][3-(3,4-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-16-1P, [5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl][3-(4-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-17-2P, [5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl][3-(3-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-18-3P, (3-Chlorophenyl)[3-(2,5-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-19-4P, [3-(3-Aminophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-chlorophenyl)amine 476638-20-7P, (3-Chlorophenyl)[3-(2,4-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-21-8P, (3-Chlorophenyl)[3-(2-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-22-9P, (3-Chlorophenyl)[3-(2-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-23-0P, (3-Chlorophenyl)[3-(3-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-24-1P, (3-Chlorophenyl)[3-(4-fluorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-25-2P, (3-Chlorophenyl)[3-(3-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-26-3P, (3-Chlorophenyl)[3-(3,4-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-27-4P, (3-Chlorophenyl)[3-(4-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-28-5P, (3-Chlorophenyl)[3-p-tolylsulfanylbenzo[g]quinoxalin-2-yl]amine 476638-29-6P, [3-(2,5-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of benzo[g]quinoxalines for use against infectious diseases)

IT 476638-30-9P, [3-(3-Aminophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-31-0P, [3-(2,4-Dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-32-1P, [3-(2-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-33-2P, [3-(2-Chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-34-3P, [3-(3-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-35-4P, [3-(4-Fluorophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-36-5P, [3-(3-Chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-37-6P, [3-(3,4-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-38-7P, [3-(4-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-39-8P, [3-(3-p-Tolylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-40-1P, [3-(3-Bromophenylsulfanyl)benzo[g]quinoxalin-2-yl](4-trifluoromethylphenyl)amine 476638-41-2P, [3-(2,5-Dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-trifluoromethylphenyl)amine 476638-42-3P, [3-(2,5-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-43-4P, [3-(3-Aminophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-44-5P, [3-(2,4-Dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-45-6P, [3-(2-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-46-7P, [3-(2-Chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-47-8P, [3-(3-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-48-9P, [3-(4-Fluorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-49-0P, [3-(3-Chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-

fluorophenyl)amine 476638-50-3P, [3-(3,4-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-51-4P, [3-(4-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-52-5P, (3-Fluorophenyl)(3-p-tolylsulfanylbenzo[g]quinoxalin-2-yl)amine 476638-53-6P, [3-(3-Bromophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-54-7P, [3-(2,5-Dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-55-8P, [3-(2,6-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl](3-fluorophenyl)amine 476638-56-9P, (4-Bromophenyl)[3-(2,5-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-57-0P, (4-Bromophenyl)[3-(3-aminophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-58-1P, (4-Bromophenyl)[3-(2,4-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-59-2P, (4-Bromophenyl)[3-(2-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-60-5P, (4-Bromophenyl)[3-(2-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-61-6P, (4-Bromophenyl)[3-(3-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-62-7P, (4-Bromophenyl)(3-phenylsulfanylbenzo[g]quinoxalin-2-yl)amine 476638-63-8P, (4-Bromophenyl)[3-(3-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-64-9P, (4-Bromophenyl)[3-(3,4-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-65-0P, (4-Bromophenyl)[3-(4-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-66-1P, (4-Bromophenyl)(3-p-tolylsulfanylbenzo[g]quinoxalin-2-yl)amine 476638-67-2P, (4-Bromophenyl)[3-(3-bromophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-68-3P, (4-Bromophenyl)[3-(2,5-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-69-4P, (4-Chlorophenyl)[3-(2,5-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-70-7P, (4-Chlorophenyl)[3-(3-aminophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-71-8P, (4-Chlorophenyl)[3-(2,4-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-72-9P, (4-Chlorophenyl)[3-(2-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-73-0P, (4-Chlorophenyl)[3-(2-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-74-1P, (4-Chlorophenyl)[3-(3-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-75-2P, (4-Chlorophenyl)[3-(4-fluorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-76-3P, (4-Chlorophenyl)[3-(3-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-77-4P, (4-Chlorophenyl)[3-(4-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-78-5P, (4-Chlorophenyl)(3-p-tolylsulfanylbenzo[g]quinoxalin-2-yl)amine 476638-79-6P, (4-Chlorophenyl)[3-(3-bromophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-80-9P, (3-Chloro-4-fluorophenyl)[3-(2,5-dichlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-81-0P, (3-Chloro-4-fluorophenyl)[3-(3-aminophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-82-1P, (3-Chloro-4-fluorophenyl)[3-(2,4-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-83-2P, (3-Chloro-4-fluorophenyl)[3-(2-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-84-3P, (3-Chloro-4-fluorophenyl)[3-(2-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-85-4P, (3-Chloro-4-fluorophenyl)[3-(3-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-86-5P, (3-Chloro-4-fluorophenyl)[3-(4-fluorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-87-6P, (3-Chloro-4-fluorophenyl)[3-(3-chlorophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-88-7P, (3-Chloro-4-fluorophenyl)[3-(4-methoxyphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-89-8P, (3-Chloro-4-fluorophenyl)(3-p-tolylsulfanylbenzo[g]quinoxalin-2-yl)amine 476638-90-1P, (3-Chloro-4-fluorophenyl)[3-(3-bromophenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-91-2P, (3-Chloro-4-fluorophenyl)[3-(2,5-dimethylphenylsulfanyl)benzo[g]quinoxalin-2-yl]amine 476638-92-3P, 2,3-Bis(3-chlorophenylsulfanyl)benzo[g]quinoxaline 476638-93-4P,

2,3-Bis(naphthalen-2-ylsulfanyl)benzo[g]quinoxaline 476638-94-5P, 2,3-Bis(4-fluorophenylsulfanyl)benzo[g]quinoxaline 476638-95-6P, 2,3-Bis(4-methoxyphenylsulfanyl)benzo[g]quinoxaline 476638-96-7P, 2,3-Bis(3,4-dichlorophenylsulfanyl)benzo[g]quinoxaline 476638-97-8P, 2,3-Bis(2,5-dichlorophenylsulfanyl)benzo[g]quinoxaline 476638-98-9P, 2,3-Bis(3-bromophenylsulfanyl)benzo[g]quinoxaline 476638-99-0P, 2,3-Bis(4-methylphenylsulfanyl)benzo[g]quinoxaline 476639-00-6P, 2,3-Bis(3-methylphenylsulfanyl)benzo[g]quinoxaline 476639-01-7P, 2,3-Bis[(5-amino-[1,3,4]oxadiazol-2-yl)sulfanyl]benzo[g]quinoxaline 476639-02-8P, 2,3-Bis[(5-(pyridin-4-yl)[1,3,4]oxadiazol-2-yl)sulfanyl]benzo[g]quinoxaline 476639-03-9P, 2,3-Bis[(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]benzo[g]quinoxaline 476639-04-0P, 2,3-Bis(2-methylphenylsulfanyl)benzo[g]quinoxaline 476639-05-1P, 2,3-Bis(2,4-dimethylphenylsulfanyl)benzo[g]quinoxaline 476639-06-2P, 2,3-Bis(3-methoxyphenylsulfanyl)benzo[g]quinoxaline 476639-07-3P, 2,3-Bis(2,5-dimethylphenylsulfanyl)benzo[g]quinoxaline 476639-08-4P, 2,3-Bis(4-aminophenylsulfanyl)benzo[g]quinoxaline 476639-09-5P, 2,3-Bis(3-aminophenylsulfanyl)benzo[g]quinoxaline 476639-10-8P, 2,3-Bis[(1H-imidazol-2-yl)sulfanyl]benzo[g]quinoxaline 476639-11-9P, 4-[3-(3-Chlorophenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-12-0P, 4-[3-(4-Methoxyphenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-13-1P, 4-[3-(4-Fluorophenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-14-2P, 4-[3-(3,4-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-15-3P, 4-[3-(2,5-Dichlorophenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-16-4P, 4-[3-(3-Bromophenylsulfanyl)benzo[g]quinoxalin-2-ylsulfanyl]phenylamine 476639-17-5P, 2-(Pyridin-4-yl)-4,13-dihydro-14-thia-1,3,3a,5,12-pentaazaazuleno[5,6-b]anthracene 476639-19-7P, Benzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-20-0P, 3-(3,4-Dimethoxyphenyl)benzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-21-1P, 2-Methyl-3-phenylbenzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-22-2P, 2,3-Diphenylbenzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-23-3P, 2,3-Di-p-tolylbenzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-24-4P, 2,3-Bis(furan-2-yl)benzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-25-5P, 2,3-Bis(4-bromophenyl)benzo[g]quinoxaline-6-sulfonic acid sodium salt 476639-27-7P, 2,3-Diphenylbenzo[g]quinoxaline-7-sulfonic acid sodium salt 476639-29-9P, 3-[3,5-Bis(trifluoromethyl)phenyl]benzo[g]quinoxaline-7-sulfonic acid sodium salt 476639-30-2P, 2,3-Bis(thiophen-3-yl)benzo[g]quinoxaline-7-sulfonic acid sodium salt 476639-31-3P, 2,3-Bis(pyridin-2-yl)benzo[g]quinoxaline-7-sulfonic acid sodium salt 476639-32-4P, 2,3-Bis(thiophen-2-yl)benzo[g]quinoxaline-7-sulfonic acid sodium salt 476639-33-5P, 2,3-Bis(4-bromophenyl)benzo[g]quinoxaline-7-sulfonamide 476639-34-6P, 2,3-Bis(thiophen-2-yl)benzo[g]quinoxaline-6-sulfonamide 476639-35-7P, 2,3-Bis(4-fluorophenyl)benzo[g]quinoxaline-6-sulfonamide 476639-36-8P, 5,10-Dibromo-2-(3-chlorophenyl)benzo[g]quinoxaline 476639-37-9P, 2-[3,5-Bis(trifluoromethyl)phenyl]-5,10-dibromobenzo[g]quinoxaline 476639-38-0P, 5,10-Dibromo-2-(3,4-dimethoxyphenyl)benzo[g]quinoxaline 476639-39-1P, 5,10-Dibromo-2-methyl-3-phenylbenzo[g]quinoxaline 476639-40-4P, 5,10-Dibromo-2,3-bis(thiophen-2-yl)benzo[g]quinoxaline 476639-41-5P, 5,10-Dibromo-2-(thiophen-3-yl)-3-(thiophen-2-yl)benzo[g]quinoxaline 476639-42-6P, 5,10-Dibromo-2,3-bis(thiophen-3-yl)benzo[g]quinoxaline 476639-43-7P, 5,10-Dibromo-2,3-bis(5-bromo-2-hydroxyphenyl)benzo[g]quinoxaline 476639-44-8P, 5,10-Dibromo-2,3-bis(furan-2-yl)benzo[g]quinoxaline 476639-45-9P, 5,10-Dibromo-2,3-bis(pyridin-2-yl)benzo[g]quinoxaline 476639-46-0P, 5,10-Dibromo-2,3-bis(3-methoxyphenyl)benzo[g]quinoxaline 476639-47-1P 476639-48-2P, 5,10-Dibromo-2,3-bis(4-methylphenyl)benzo[g]quinoxaline

476639-49-3P, 5,10-Dibromo-2,3-bis(4-bromophenyl)benzo[g]quinoxaline
476639-50-6P, 5,10-Dibromo-2,3-bis(4-fluorophenyl)benzo[g]quinoxaline
476639-51-7P, 5,10-Dibromo-2,3-bis(4-methoxyphenyl)benzo[g]quinoxaline
476639-52-8P, [5-[5,10-Dibromo-3-(5-methoxycarbonylmethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid methyl ester
476639-53-9P, [5-[5,10-Dibromo-3-(4-methoxycarbonylmethylthiophen-2-yl)benzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid methyl ester
476639-54-0P, 2,3-Bis(thiophen-2-yl)-1,2,3,4-tetrahydrobenzo[g]quinoxaline
476639-55-1P, 3-[5-[3-[5-(2-Carboxyethyl)thiophen-2-yl]-1,2,3,4-tetrahydrobenzo[g]quinoxalin-2-yl]thiophen-2-yl]propionic acid
476639-56-2P, 3-(Thiophen-2-yl)-3,4-dihydro-1H-benzo[g]quinoxalin-2-one
476639-57-3P, [5-[3-(5-Carboxymethylthiophen-2-yl)-1,2,3,4-tetrahydrobenzo[g]quinoxalin-2-yl]thiophen-2-yl]acetic acid
476639-58-4P, 2-[3,5-Bis(trifluoromethyl)phenyl]benzo[g]quinoxaline N-oxide 476639-60-8P, 2,3-Bis(4-fluorophenyl)benzo[g]quinoxaline 1,4-dioxide 476639-61-9P, 2-Amino-1-[2-(thiophen-2-yl)ethyl]-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-62-0P, 2-Amino-1-(2-hydroxyethyl)-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-63-1P, 2-Amino-1-(3-methylbutyl)-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-64-2P, 2-Amino-1-(2-hydroxypropyl)-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-65-3P, 2-Amino-1-[2-(3-fluorophenyl)ethyl]-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-66-4P, 2-Amino-1-[2-(3-chlorophenyl)ethyl]-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-67-5P, 2-Amino-1-[2-(4-methoxyphenyl)ethyl]-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-68-6P, 2-Amino-1-(2-cyclohex-1-enylethyl)-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-69-7P, 2-Amino-1-(3-(imidazol-1-yl)propyl)-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carbonitrile 476639-70-0P, 1-(2-Hydroxyethyl)-2-oxo-2,3-dihydro-1H-benzo[g]pyrrolo[2,3-b]quinoxaline-3-carboxylic acid ethyl ester 476639-71-1P, 2-(2,3-Dihydro-1-oxa-4,5,12-triazanaphthacen-4-yl)ethanol 476639-72-2P, 2-[2-(2,4-Dichlorophenyl)vinyl]-3-(thiophen-2-yl)benzo[g]quinoxaline 476639-73-3P, 1,2,3,4-Tetrahydrobenzo[b]phenazine 476639-74-4P, 2-[5-(Pyridin-4-yl)-1H-[1,2,4]triazole-3-ylsulfanyl]benzo[g]quinoxaline 476639-75-5P, 2-[(1H-Benzimidazole-2-yl)sulfanyl]benzo[g]quinoxaline 476639-76-6P, 2-(4-Nitrophenyl)benzo[g]quinoxaline 476639-77-7P, 2-Phenyl-3-trifluoromethylbenzo[g]quinoxaline 476639-78-8P, 2-Methyl-3-phenylbenzo[g]quinoxaline 476639-79-9P, 2,3-Bis(4-bromophenyl)benzo[g]quinoxaline 476639-80-2P, 2-(4-Fluorophenyl)benzo[g]quinoxaline
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of benzo[g]quinoxalines for use against infectious diseases)

IT 88201-45-0, Gene INSR tyrosine kinase **98037-52-6, Abl** tyrosine **kinase** 141349-89-5, Src tyrosine kinase 148640-14-6, Protein kinase Akt 160477-78-1, Protein kinase SRPK1 204784-44-1, Protein kinase SRPK2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human, **inhibitors**; preparation of benzo[g]quinoxalines for use against infectious diseases)

IT 9032-92-2, Glycosidase
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(inhibitors; combined with benzo[g]quinoxalines for use against infectious diseases)

IT 61246-68-2D, L-DdA, prodrug
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prodrug; combined with benzo[g]quinoxalines for use against infectious

diseases

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ACCESSION NUMBER: 2002:158405 HCAPLUS Full-text
DOCUMENT NUMBER: 136:200113
TITLE: 3-Cyanoquinolines, 3-cyano-1,6-naphthyridines, and 3-cyano-1,7-naphthyridines as protein kinase inhibitors
INVENTOR(S): Boschelli, Diane Harris; Wang, Yanong; Boschelli, Frank Charles; Berger, Dan Maarten; Zhang, Nan; Powell, Dennis William; Ye, Fei; Yamashita, Ayako; Demorin, Frenel Fils; Wu, Biqi; Tsou, Hwei-ru; Overbeek-Klumpers, Elsebe Geraldine; Wissner, Allan
PATENT ASSIGNEE(S): American Home Products Corporation, USA; Wyeth
SOURCE: U.S. Pat. Appl. Publ., 172 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002026052	A1	20020228	US 2001-820070		20010328
US 6521618	B2	20030218			
US 6689772	B1	20040210	US 2002-318213		20021212
US 2004176602	A1	20040909	US 2004-755136		20040109
PRIORITY APPLN. INFO.:			US 2000-219322P	P	20000328
			US 2001-820070	A3	20010328
			US 2002-318213	A3	20021212

OTHER SOURCE(S): MARPAT 136:200113

AB Title compds. I [X = N(H) or substituted derivs., O, SO0-2; n = 0-1; A = divalent (un)substituted alkyl, C(O), C(O)-alkyl, alkyl-C(O), cycloalkyl, or absent; T, Z = C, N provided that both T and Z are not N; R1 = cycloalkyl, 5-6 atom (hetero)aryl ring containing 0-4 heteroatoms, 8-20 atom bicyclic heteroaryl ring containing 1-4 heteroatoms, etc.; R2a-c = H, aryl, CH2-aryl, O-aryl, SO0-2-aryl, NO2, SH, etc.; R3 = alkenyl, alkynyl, (hetero)aryl; R4 = (un)substituted alkyl, alkenyl, alkynyl, (hetero)aryl] were prepared Over 500 synthetic examples were disclosed, including some combinatorial prepns., and addnl. reference examples. E.g., 4-[(4-bromo-2-thienyl)methyl]morpholine reacted with bis(pinacolato)diboron [DMSO, PdCl2(dppf), KOAc] to give dioxaborolane II. II was coupled to 7-bromo-4-[3-chloro-4-[(1-methyl-1H-imidazol-2- yl)sulfanyl]anilino]-3-quinolinecarbonitrile [preparation given; diglyme, Pd(PPh3)4, NaHCO3] to yield invention compound III as a yellow solid after purification III had IC50 = 6.0 nM for Raf1 kinase and inhibited the human adenocarcinoma CaCo-2 cell line with IC50 = 1.9, 0.78 (2 trials). I are useful as antineoplastic agents, and in the treatment of osteoporosis and polycystic kidney disease.

IC ICM C07D471-02
INCL 546122000
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7, 28
IT Antiarthritics
Antitumor agents
Antiviral agents
Cytotoxic agents
Immunosuppressants
(preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)
IT 364788-53-4P 364795-34-6P

RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 364789-63-9P 364789-65-1P 364789-67-3P 364789-69-5P 364789-71-9P
364789-73-1P 364789-75-3P 364789-77-5P 364789-79-7P 364789-81-1P
364789-84-4P 364789-86-6P 364789-88-8P 364789-91-3P 364789-94-6P
364789-97-9P 364789-99-1P 364790-01-2P 364790-06-7P 364790-09-0P
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364790-41-0P 364790-44-3P 364790-46-5P 364790-48-7P 364790-49-8P
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364790-89-6P 364790-90-9P 364790-91-0P 364790-92-1P 364790-93-2P
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RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

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PAC (Pharmacological activity); THU (Therapeutic use);
BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation);
USES (Uses)
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364796-33-8P
RL: BSU (Biological study, unclassified); **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 364788-97-6P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); **PAC (Pharmacological activity)**; RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

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RL: **PAC (Pharmacological activity)**; RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 9026-43-1 79079-06-4, EGFr kinase 80449-02-1 98037-52-6
114051-78-4, Lck kinase 125149-26-0, FGF receptor kinase 137632-06-5, Csk protein kinase 137632-09-8, ErbB-2 kinase 138674-26-7, Syk kinase 139691-76-2, Raf1 kinase 139691-76-2, Raf kinase 140208-17-9, Lyn kinase 141349-89-5, Src kinase 141349-91-9, Yes protein kinase 141436-78-4, Protein kinase C 142008-29-5, Protein kinase A 142243-02-5 142805-58-1, Mek kinase 143597-35-7, UL-97 kinase 144114-16-9, Fak protein tyrosine kinase 144697-17-6, c-Src kinase 147014-95-7, ErbB-3 kinase 148047-29-4, Tie-2 kinase 148047-34-1, Zap-70 kinase 148640-14-6, Protein kinase B 149433-92-1, EPH kinase 150027-21-7, PDGF-RA receptor tyrosine kinase 150428-23-2 150977-45-0, Gene KDR protein kinase 151769-13-0, Receptor tyrosine kinase Tie-1 152743-99-2, Gene erbB-4 protein kinase 161384-16-3, Jak kinase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(**inhibitors**; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase **inhibitors**)

L66 ANSWER 19 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:730706 HCAPLUS Full-text
DOCUMENT NUMBER: 135:288703
TITLE: 3-Cyanoquinolines, 3-cyano-1,6-naphthyridines, and 3-cyano-1,7-naphthyridines as protein kinase inhibitors
INVENTOR(S): Boschelli, Diane Harris; Wang, Yanong; Boschelli, Frank Charles; Berger, Dan Maarten; Zhang, Nan; Powell, Dennis William; Ye, Fei; Yamashita, Ayako;

Deporin, Prenel Fils.; Wu, Bigi; Tsou, Hwei-ru; Overbeek-klumpers, Elsebe Geraldine; Wissner, Allan
PATENT ASSIGNEE(S): American Home Products Corporation, USA
SOURCE: PCT Int. Appl., 448 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001072711	A1	20011004	WO 2001-US9966		20010328
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2404662	AA	20011004	CA 2001-2404662		20010328
EP 1268431	A1	20030102	EP 2001-924407		20010328
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BR 2001009650	A	20030422	BR 2001-9650		20010328
JP 2003528857	T2	20030930	JP 2001-570624		20010328
PRIORITY APPLN. INFO.:			US 2000-535843	A	20000328
			WO 2001-US9966	W	20010328

OTHER SOURCE(S): MARPAT 135:288703

AB Title compds. I [X = N(H) or substituted derivs., O, SO0-2; n = 0-1; A = divalent (un)substituted alkyl, C(O), C(O)-alkyl, alkyl-C(O), cycloalkyl, or absent; T, Z = C, N provided that both T and Z are not N; R1 = cycloalkyl, 5-6 atom (hetero)aryl ring containing 0-4 heteroatoms, 8-20 atom bicyclic heteroaryl ring containing 1-4 heteroatoms, etc.; R2a-c = H, aryl, CH2-aryl, O-aryl, SO0-2-aryl, NO2, SH, etc.; R3 = alkenyl, alkynyl, (hetero)aryl; R4 = (un)substituted alkyl, alkenyl, alkynyl, (hetero)aryl] were prepared Over 500 synthetic examples were disclosed, including some combinatorial prepns., and addnl. reference examples. E.g., 4-[(4-bromo-2-thienyl)methyl]morpholine reacted with bis(pinacolato)diboron [DMSO, PdCl2(dppf), KOAc] to give dioxaborolane II. II was coupled to 7-bromo-4-[3-chloro-4-[(1-methyl-1H-imidazol-2- yl)sulfanyl]anilino]-3-quinolinecarbonitrile [preparation given; diglyme, Pd(PPh3)4, NaHCO3] to yield invention compound III as a yellow solid after purification III had IC50 = 6.0 nM for Raf1 kinase and inhibited the human adenocarcinoma CaCo-2 cell line with IC50 = 1.9, 0.78 (2 trials). I are useful as antineoplastic agents, and in the treatment of osteoporosis and polycystic kidney disease.

IC ICM C07D215-54
ICS C07D409-04; C07D401-04; C07D401-06; C07D405-04; C07D405-14; C07D409-14; C07D401-12; C07D401-10; C07D401-14; C07D405-12; C07D471-04; A61K031-4706; A61K031-4709; A61P035-00; C07D471-04; C07D221-00; C07D221-00
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7, 28

IT Antiarthritics
Antitumor agents
Antiviral agents
Cytotoxic agents
Immunosuppressants

(preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 364787-81-5P 364788-56-7P 364788-58-9P 364788-62-5P 364788-75-0P
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364795-18-6P
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
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(2R)-1-[[5-[3-Cyano-4-(2,4-dichloro-5-methoxyanilino)-7-quinolinyl]-2-furyl]methyl]-2-pyrrolidinecarboxamide 364788-68-1P 364788-70-5P
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364791-29-7P 364791-30-0P 364791-31-1P 364791-32-2P 364791-33-3P
364791-34-4P 364791-35-5P 364791-36-6P 364791-37-7P 364791-38-8P
364791-39-9P 364791-40-2P 364791-41-3P 364791-42-4P 364791-43-5P
364791-44-6P 364791-45-7P 364791-46-8P 364791-47-9P 364791-48-0P
364791-49-1P 364791-50-4P 364791-51-5P 364791-52-6P 364791-53-7P
364791-54-8P 364791-55-9P 364791-56-0P 364791-57-1P 364791-58-2P

364791-59-3P 364791-60-6P 364791-61-7P 364791-62-8P 364791-63-9P 364791-64-0P 364791-65-1P 364791-66-2P 364791-67-3P 364791-68-4P
364791-69-5P 364791-70-8P 364791-71-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 364791-72-0P 364791-73-1P 364791-74-2P 364791-75-3P 364791-76-4P
364791-77-5P 364791-78-6P 364791-79-7P 364791-80-0P 364791-81-1P
364791-82-2P 364791-83-3P 364791-84-4P 364791-85-5P 364791-86-6P
364791-87-7P 364791-88-8P 364791-89-9P 364791-90-2P 364791-91-3P
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364795-07-3P 364795-08-4P 364795-10-8P 364795-12-0P 364795-13-1P
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364795-38-0P 364795-39-1P 364795-40-4P 364795-41-5P 364795-42-6P
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364795-48-2P 364795-49-3P 364795-50-6P 364795-51-7P 364795-52-8P
364795-53-9P 364795-54-0P 364795-55-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 364795-56-2P 364795-57-3P 364795-58-4P 364795-59-5P 364795-60-8P
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364795-92-6P 364795-93-7P 364795-94-8P 364795-95-9P 364795-96-0P
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364796-17-8P 364796-18-9P 364796-19-0P 364796-20-3P 364796-21-4P
364796-22-5P 364796-23-6P 364796-24-7P 364796-25-8P 364796-26-9P
364796-27-0P 364796-28-1P 364796-29-2P 364796-31-6P 364796-32-7P
364796-33-8P
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase inhibitors)

IT 9026-43-1 79079-06-4, EGFr kinase 80449-02-1 **98037-52-6**
114051-78-4, Lck kinase 125149-26-0, FGF receptor kinase 137632-06-5, Csk protein kinase 137632-09-8, erbB-2 kinase 138674-26-7, Syk kinase 139691-76-2, Raf kinase 139691-76-2, Raf1 kinase 140208-17-9, Lyn kinase 141349-89-5, Src kinase 141349-91-9, Yes protein kinase 141436-78-4, Protein kinase C 142008-29-5, Protein kinase A 142243-02-5 142805-58-1, Mek kinase 143597-35-7, UL-97 kinase 144114-16-9, Fak protein tyrosine kinase 144697-17-6, c-Src kinase 147014-95-7, erbB-3 kinase 148047-29-4, tie-2 kinase 148047-34-1, Zap-70 kinase 148640-14-6, Protein kinase B 149433-92-1, EPH kinase 150027-21-7, PDGF-RA receptor tyrosine kinase 150428-23-2 150977-45-0, Gene KDR protein kinase 151769-13-0, Receptor tyrosine kinase Tie-1 152743-99-2, Gene erbB-4 protein kinase 161384-16-3, Jak kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**inhibitors**; preparation of cyanoquinolines and cyanonaphthyridines as protein kinase **inhibitors**)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 20 OF 88 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:799946 HCAPLUS Full-text
DOCUMENT NUMBER: 128:110534
TITLE: Bcr-abl translocation can occur during the induction of multidrug resistance and confers apoptosis resistance on myeloid leukemic cell lines
AUTHOR(S): Belloc, Francis; Cotteret, Sophie; Labroille, Gilles; Schmit, Valerie; Jaloustre, Claudine; Dumain, Patrice; Durrieu, Francoise; Reiffers, Josy; Boisseau, Michel R.; Bernard, Philippe; Lacombe, Francis
CORPORATE SOURCE: Laboratoire d'Hematologie, Hopital haut Leveque, Pessac, 33604, Fr.
SOURCE: Cell Death and Differentiation (1997), 4(8), 806-814
CODEN: CDDIEK; ISSN: 1350-9047
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Apoptosis was studied in parental and mdr 1 expressing U937, HL60 and K562 myeloid leukemic cell lines using mdr unrelated inducers of apoptosis such as Ara-C, cycloheximide, serum deprivation, ceramide, monensin and UV irradiation Apoptosis was efficiently induced by all these treatments in U937 and HL60 cells while K562 cells exhibited an apoptosis-resistant phenotype except with UV and monensin. The pattern of apoptosis resistance in mdr-1 expressing U937 (U937-DR) and HL60 (HL60-DR100) was similar to that presented by K562. This apoptosis-resistant phenotype of mdr cells was not overcome by concns. of verapamil inhibiting the P-gp 170 pump. The acquisition of this phenotype was posterior to the mdr-1 expressing phenotype since a HL60-DR5 variant, selected at the beginning of the induction of resistance, presented a low level of mdr-1 expression without resistance to apoptosis. The variations observed in the Fas (CD95) expression between sensitive and resistant cells were not sufficient to account for apoptosis resistance. However, a high expression in Abl antigen was found in all the apoptosis-resistant cells. RT-PCR and Western blot anal. showed that this increase in Abl antigen content was accompanied by the expression in U937-DR and HL60-DR100 cells of a hybrid bcr/abl mRNA and a 210 kDa Bcr/Abl protein which was constitutive in K562. This expression was due to the translocation of abl and the amplification of the bcr-abl translocated gene. These results are in agreement with the role of Bcr/**Abl** tyrosine protein **kinase** as an **inhibitor** of apoptosis independently of the mdr-1 expression. They also suggest that translocation of the abl gene in the bcr region is a highly probable rearrangement in the mdr-1 expressing myeloid cells and that bcr/Abl tyrosine kinase effect on apoptosis needs the regulation of intracellular pH and is inactive against UV-induced apoptosis.

CC 1-6 (Pharmacology)
Section cross-reference(s): 3, 14

IT Ceramides
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(bcr-abl translocation can occur during the induction of multidrug resistance and confers apoptosis resistance on myeloid leukemic cell lines)

IT 66-81-9, Cycloheximide 147-94-4, Ara-C **17090-79-8**, Monensin
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(bcr-abl translocation can occur during the induction of multidrug resistance and confers apoptosis resistance on myeloid leukemic cell lines)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L66 ANSWER 21 OF 88 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 89193419 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2539083
TITLE: A truncated v-abl-derived tyrosine-specific tyrosine kinase expressed in **Escherichia** coli.
AUTHOR: Pritchard M L; Rieman D; Feild J; Kruse C; Rosenberg M; Poste G; Greig R G; Ferguson B Q
CORPORATE SOURCE: Department of Cell Biology, Smith Kline and French Laboratory, Philadelphia, PA.
SOURCE: The Biochemical journal, (1989 Jan 15) Vol. 257, No. 2, pp. 321-9.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904

ENTRY DATE: Entered STN: 6 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 21 Apr 1989

AB Several biochemical properties of a 43 kDa v-abl-encoded tyrosine-specific protein kinase (p43v-abl) expressed in **Escherichia** coli were examined. p43v-abl is a fragment of a 60 kDa v-abl-encoded precursor, p60v-abl, and could be generated by limited proteolysis of a purified p60v-abl with trypsin. Tryptic cleavage of p60v-abl was prevented in the presence of ATP. These results suggest that the catalytic kinase domain of v-abl-derived protein can be separated from other (regulatory) domains by limited proteolysis. p43v-abl readily phosphorylated tyrosine residues on several different protein and peptide substrates, including peptides containing only two amino acid residues. However, the local sequence of the tyrosine-containing peptide substrate significantly affected its rate of phosphorylation. Thus the primary structure and local conformation at the tyrosine acceptor site can play an important role in determining the substrate specificity of v-abl-derived kinase. Phosphorylation by p43v-abl requires Mn2+, Co2+ or Mg2+ and exhibits a strong preference for ATP as phosphate donor. Analogues of ATP and the thiol-reactive reagent N-ethylmaleimide **inhibited p43v-abl kinase** activity. Purified p43v-abl is intrinsically thermolabile (t1/2 = 5 min at 40 degrees C) and phosphorylates glycerol inefficiently (Km = 1.4 M).

CT *Abelson murine leukemia virus: EN, enzymology
Abelson murine leukemia virus: GE, genetics
Electrophoresis, Polyacrylamide Gel
Escherichia coli
Genes, Viral
Heat
*Leukemia Virus, Murine: EN, enzymology
Metals: ME, metabolism
*Oncogenes
Peptides: ME, metabolism
Phosphorylation
Plasmids
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Protein-Tyrosine Kinase: IP, isolation & purification
*Protein-Tyrosine Kinase: ME, metabolism
*Transfection

CN 0 (Metals); 0 (Peptides); EC 2.7.1.112 (Protein-Tyrosine Kinase)

L66 ANSWER 22 OF 88 MEDLINE on STN
ACCESSION NUMBER: 2006149244 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16537444
TITLE: Structural characterization of autoinhibited c-Met kinase produced by coexpression in bacteria with phosphatase.
AUTHOR: Wang Weiru; Marimuthu Adhirai; Tsai James; Kumar Abhinav; Krupka Heike I; Zhang Chao; Powell Ben; Suzuki Yoshihisa; Nguyen Hoa; Tabrizizad Maryam; Luu Catherine; West Brian L
CORPORATE SOURCE: Plexxikon, Inc., 91 Bolivar Drive, Berkeley, CA 94710, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2006 Mar 7) Vol. 103, No. 10, pp. 3563-8. Electronic Publication: 2006-02-28.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-2G15
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 16 Mar 2006
Last Updated on STN: 18 Apr 2006

Entered Medline: 17 Apr 2006.

AB Protein kinases are a large family of cell signaling mediators undergoing intensive research to identify inhibitors or modulators useful for medicine. As one strategy, small-molecule compounds that bind the active site with high affinity can be used to inhibit the enzyme activity. X-ray crystallography is a powerful method to reveal the structures of the kinase active sites, and thus aid in the design of high-affinity, selective inhibitors. However, a limitation still exists in the ability to produce purified kinases in amounts sufficient for crystallography. Furthermore, kinases exist in different conformation states as part of their normal regulation, and the ability to prepare crystals of kinases in these various states also remains a limitation. In this study, the c-Abl, c-Src, and c-Met kinases are produced in high yields in **Escherichia** coli by using a bicistronic vector encoding the PTP1B tyrosine phosphatase. A 100-fold lower dose of the inhibitor, Imatinib, was observed to **inhibit** the unphosphorylated form of c- **Abl kinase** prepared by using this vector, compared to the phosphorylated form produced without PTP1B, consistent with the known selectivity of this inhibitor for the unactivated conformation of the enzyme. Unphosphorylated c-Met kinase produced with this vector was used to obtain the crystal structure, at 2.15-A resolution, of the autoinhibited form of the kinase domain, revealing an intricate network of interactions involving c-Met residues documented previously to cause dysregulation when mutated in several cancers.

CT Amino Acid Sequence
Base Sequence
Crystallography, X-Ray
DNA: GE, genetics
Escherichia coli: GE, genetics
Gene Expression
Genetic Vectors
Models, Molecular
Mutation
Neoplasms: EN, enzymology
Neoplasms: GE, genetics
Phosphotransferases: BI, biosynthesis
Phosphotransferases: GE, genetics
Protein Structure, Tertiary
Protein-Tyrosine-Phosphatase: GE, genetics
Proto-Oncogene Proteins: BI, biosynthesis
Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins c-abl: BI, biosynthesis
Proto-Oncogene Proteins c-abl: GE, genetics
Proto-Oncogene Proteins c-met: AI, antagonists & inhibitors
Proto-Oncogene Proteins c-met: BI, biosynthesis
*Proto-Oncogene Proteins c-met: CH, chemistry
Proto-Oncogene Proteins c-met: GE, genetics
Recombinant Proteins: AI, antagonists & inhibitors
Recombinant Proteins: BI, biosynthesis
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics

RN 9007-49-2 (DNA)

CN 0 (Proto-Oncogene Proteins); 0 (Recombinant Proteins); EC 2.7 (Phosphotransferases); EC 2.7.1.112 (Proto-Oncogene Proteins c-abl); EC 2.7.1.112 (Proto-Oncogene Proteins c-met); EC 2.7.10.2 (CSK protein, human); EC 3.1.3.48 (Protein-Tyrosine-Phosphatase); EC 3.1.3.48 (protein tyrosine phosphatase 1B)

L66 ANSWER 23 OF 88 MEDLINE on STN
ACCESSION NUMBER: 2005606456 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16286749
TITLE: Severe pustular eruption associated with imatinib and

...azole in a patient with chron... myeloid leukemia.
AUTHOR: Gambillara E; Laffitte E; Widmer N; Decosterd L A; Buchonal M A; Kovacsovics T; Panizzon R G
CORPORATE SOURCE: Dermatology Sevices, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
SOURCE: Dermatology (Basel, Switzerland), (2005) Vol. 211, No. 4, pp. 363-5.
Journal code: 9203244. ISSN: 1018-8665.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 28 Jan 2006
Entered Medline: 27 Jan 2006

AB Imatinib is a specific and potent **inhibitor** of the BCR- **ABL** tyrosine **kinase**. Several clinical trials have demonstrated the efficacy of imatinib in chronic myeloid leukemia. Adverse cutaneous reactions induced by imatinib are frequent and may be dose related. We report a case of an unusual pustular eruption in a patient with chronic myeloid leukemia, who received high doses imatinib for blast crisis and later voriconazole for invasive pulmonary aspergillosis. At the time of his skin eruption, elevated plasma levels of imatinib were recorded. Imatinib is primarily metabolized by the cytochrome CYP3A4. Voriconazole is a cytochrome CYP3A4 inhibitor and can lead to high plasma levels of imatinib. This case suggests that severe drug reactions to imatinib may be related not only to imatinib doses, but also to elevated plasma drug levels resulting from pharmacokinetic interactions. The monitoring of imatinib plasma levels may be of help for identifying patients at risk for severe toxicity. Copyright 2005 S. Karger AG, Basel.

CT Check Tags: Male
Adult
***Antifungal Agents: AE, adverse effects**
*Antineoplastic Agents: AE, adverse effects
Antineoplastic Agents: BL, blood
Aspergillosis: DT, drug therapy
Cytochrome P-450 Enzyme System: AI, antagonists & inhibitors
*Drug Eruptions: ET, etiology
Drug Interactions
Enzyme Inhibitors: AE, adverse effects
*Exanthema: CI, chemically induced
Humans
*Irritants: AE, adverse effects
*Leukemia, Myeloid, Chronic: DT, drug therapy
Lung Diseases, Fungal: DT, drug therapy
*Piperazines: AE, adverse effects
Piperazines: BL, blood
*Protein-Tyrosine Kinase: AI, antagonists & inhibitors
*Pyrimidines: AE, adverse effects
Pyrimidines: BL, blood
*Triazoles: AE, adverse effects

RN 152459-95-5 (imatinib); 9035-51-2 (Cytochrome P-450 Enzyme System)
CN 0 (Antifungal Agents); 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Irritants); 0 (Piperazines); 0 (Pyrimidines); 0 (Triazoles); 0 (voriconazole); EC 1.14.14.1 (CYP3A protein, human); EC 2.7.1.112 (Protein-Tyrosine Kinase)

L66 ANSWER 24 OF 88 MEDLINE on STN
ACCESSION NUMBER: 2005163005 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15795113 ... STN ...
TITLE: Immunohistochemical characterization of cutaneous drug eruptions by STI571.
AUTHOR: Park Hyun Jeong; Kim Hei Sung; Kim Hee Jung; Lee Jun Young; Cho Baik Kee; Lee Ah Won; Yoon Do Young; Cho Dae Ho
CORPORATE SOURCE: Department of Dermatology, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 62 Youido-dong, Seoul 150-713, South Korea.. hjpark@catholic.ac.kr
SOURCE: Journal of dermatological science, (2005 Apr) Vol. 38, No. 1, pp. 9-15.
Journal code: 9011485. ISSN: 0923-1811.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 30 Mar 2005
Last Updated on STN: 8 Sep 2005
Entered Medline: 7 Sep 2005

AB BACKGROUND: STI571, a selective BCR-ABL tyrosine kinase inhibitor, is a promising new drug for chronic myelogenous leukemia (CML). However, the drug has been reported to be associated with adverse cutaneous drug eruptions with high frequency. OBJECTIVE: In this study, the characteristics of the cutaneous drug eruptions by STI571 were investigated. METHODS: The clinical records of 10 patients diagnosed with drug eruption by STI571 were reviewed. We obtained 10 skin biopsy specimens from patients with drug eruption by STI571, 6 from the antibiotics-induced drug eruption group, and 5 from normal skin (control). Immunohistochemical analysis was performed to detect CD4, CD8, CD56, IL-18, IL-1beta and ICAM-1 expression in the cutaneous drug eruption. RESULTS: Seven out of 10 patients had maculopapular exanthema, 2/10 erythema multiforme, 1/10 urticaria. We analyzed the composition of T-lymphocyte subsets from the infiltrates at the STI571-induced drug eruption site in eight patients. Unlike other drug eruptions, the increase in the CD8 expression was statistically significant, especially in the dermoepidermal junction and the upper dermis ($P < 0.01$). The enhanced expression of IL-18 and IL-1beta was observed as well. In contrast, ICAM-1 was either weakly positive or negative. CONCLUSION: Drug eruption caused by STI571 was mostly expressed as a maculopapular exanthema. The histopathological findings were similar in drug eruption by antibiotics or STI571. Unlike the drug eruptions caused by antibiotics, where the expression of CD4 was dominant, CD8 was dominant in drug eruptions by STI571. The expression of IL-18 and IL-1beta was increased in both groups. This elevation of IL-18 and IL-1beta may assist in understanding the pathogenesis of cutaneous drug eruption.

CT Check Tags: Female; Male
Adult
Anti-Bacterial Agents: AE, adverse effects
Case-Control Studies
Child
*Drug Eruptions: ME, metabolism
*Drug Eruptions: PA, pathology
Humans
Immunohistochemistry
Immunophenotyping
Interleukin-1: ME, metabolism
Interleukin-18: ME, metabolism
Middle Aged
*Pyrimidines: AE, adverse effects
Research Support, Non-U.S. Gov't
Skin: ME, metabolism
Skin: PA, pathology

(Anti-Bacterial Agents); 0 (Interleukin-1); 0 (Interleukin-18); 0 (Pyrimidines); 0 (ST 1571)

L66 ANSWER 25 OF 88 MEDLINE on STN
ACCESSION NUMBER: 2004038225 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14738154
TITLE: Aminopeptidase inhibitors inhibit proliferation and induce apoptosis of K562 and STI571-resistant K562 cell lines through the MAPK and GSK-3beta pathways.
AUTHOR: Sawafuji Kanoko; Miyakawa Yoshitaka; Weisberg Ellen; Griffin James D; Ikeda Yasuo; Kizaki Masahiro
CORPORATE SOURCE: Department of Internal Medicine, Keio University School of Medicine, Tokyo 160-8582, Japan.
SOURCE: Leukemia & lymphoma, (2003 Nov) Vol. 44, No. 11, pp. 1987-96.
Journal code: 9007422. ISSN: 1042-8194.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 24 Jan 2004
Last Updated on STN: 3 Mar 2004
Entered Medline: 2 Mar 2004

AB A tyrosine kinase inhibitor, STI571, has been demonstrated to be effective for the treatment of chronic myelogenous leukemia (CML). STI571 **inhibits** tyrosine **kinase** activity of **ABL** and induces apoptosis of CML cells. However, drug resistance develops commonly in patients with blast phase CML, and has become a significant therapeutic problem. We examined the effects of aminopeptidase inhibitors on CML cell line (K562) and a STI571-resistant subline of K562. Ubenimex and the more potent aminopeptidase inhibitor, actinonin, inhibited proliferation of both K562 cells and STI571-resistant K562 cells and also induced their apoptosis in dose- and time-dependent manners. Ubenimex and actinonin induced the activation of caspase-3, and the induction of apoptosis was inhibited by pan-caspase inhibitor, indicating this apoptosis is caspase-dependent. We found that serine phosphorylation of both MAPK and glycogen synthase kinase-3beta were suppressed by aminopeptidase inhibitors in parent K562 and STI571-resistant K562 cells. The expression level of cyclin D1 protein was also reduced by ubenimex and actinonin in both cell lines. These results indicated STI571-resistance does not confer the cross-resistance to aminopeptidase inhibitors in K562 cells and revealed the new findings of aminopeptidase inhibitor-induced intracellular signaling pathways.

CT *Aminopeptidases: AI, antagonists & inhibitors
Anti-Bacterial Agents: PD, pharmacology
Antineoplastic Agents: PD, pharmacology
*Apoptosis: DE, drug effects
Caspases: ME, metabolism
Cell Division: DE, drug effects
Comparative Study
Cyclin D1: ME, metabolism
Drug Resistance, Neoplasm
Enzyme Activation
*Glycogen Synthase Kinase 3: ME, metabolism
Humans
Hydroxamic Acids: PD, pharmacology
K562 Cells: DE, drug effects
K562 Cells: ME, metabolism
*Leucine: AA, analogs & derivatives
Leucine: PD, pharmacology
Leukemia, Myeloid, Chronic: ME, metabolism

Leukemia, Myeloid, Chronic: PA, pathology
*Mitogen Activated Protein Kinases: ME, metabolism
Phosphorylation: DE, drug effects
*Piperazines: PD, pharmacology
*Protease Inhibitors: PD, pharmacology
*Pyrimidines: PD, pharmacology
Research Support, Non-U.S. Gov't
Serine: CH, chemistry
Signal Transduction: DE, drug effects
RN 13434-13-4 (actinonin); 136601-57-5 (Cyclin D1); 152459-95-5 (imatinib); 56-45-1 (Serine); 58970-76-6 (bestatin); 61-90-5 (Leucine)
CN 0 (Anti-Bacterial Agents); 0 (Antineoplastic Agents); 0 (Hydroxamic Acids); 0 (Piperazines); 0 (Protease Inhibitors); 0 (Pyrimidines); EC 2.7.1.37 (Glycogen Synthase Kinase 3); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (glycogen synthase kinase 3 beta); EC 3.4.11 (Aminopeptidases); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3)

L66 ANSWER 26 OF 88 MEDLINE on STN
ACCESSION NUMBER: 2001105985 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11010972
TITLE: BCR/ABL regulates expression of the cyclin-dependent kinase inhibitor p27Kip1 through the phosphatidylinositol 3-Kinase/AKT pathway.
AUTHOR: Gesbert F; Sellers W R; Signoretti S; Loda M; Griffin J D
CORPORATE SOURCE: Department of Adult Oncology, Dana Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.
SOURCE: The Journal of biological chemistry, (2000 Dec 15) Vol. 275, No. 50, pp. 39223-30.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 18 Jan 2003
Entered Medline: 8 Feb 2001

AB Deregulation of cell cycle checkpoints is an almost universal abnormality in human cancers and is most often due to loss-of-function mutations of tumor suppressor genes such as Rb, p53, or p16(INK4a). In this study, we demonstrate that BCR/ABL inhibits the expression of a key cell cycle inhibitor, p27(Kip1), by signaling through a pathway involving phosphatidylinositol 3-kinase (PI3K). p27(Kip1) is a widely expressed inhibitor of cdk2, an essential cell cycle kinase regulating entry into S phase. We demonstrate that the decrease of p27(Kip1) is directly due to BCR/ABL in hematopoietic cells by two different approaches. First, induction of BCR/ABL by a tetracycline-regulated promoter is associated with a reversible down-regulation of p27(Kip1). Second, **inhibition** of BCR/**ABL kinase** activity with the **Abl** tyrosine **kinase inhibitor** STI571 rapidly increases p27(Kip1) levels. The PI3K inhibitor LY-294002 blocks the ability of BCR/ABL to induce p27(Kip1) down-regulation and inhibits BCR/ABL-induced entry into S phase. The serine/threonine kinase AKT/protein kinase B is a known downstream target of PI3K. Transient expression of an activated mutant of AKT was found to decrease expression of p27(Kip1), even when PI3K was inhibited by LY-294002. The mechanism of p27(Kip1) regulation is primarily related to protein stability, since inhibition of proteasome activity increased p27(Kip1) levels in BCR/ABL-transformed cells, whereas very little change in p27 transcription was found. Overall, these data are consistent with a model in which BCR/ABL suppresses p27(Kip1) protein levels through PI3K/AKT, leading to accelerated

entry into S phase. This activity is likely to explain in part previous studies showing that activation of PI3K was required for optimum transformation of hematopoietic cells by BCR/ABL in vitro and in vivo.

CT *1-Phosphatidylinositol 3-Kinase: ME, metabolism
Animals
Anti-Bacterial Agents: PD, pharmacology
Cell Cycle
*Cell Cycle Proteins
Cell Line
Cell Separation
Chromones: PD, pharmacology
Cyclin-Dependent Kinase Inhibitor p27
Cycloheximide: PD, pharmacology
Dose-Response Relationship, Drug
*Down-Regulation
Doxycycline: PD, pharmacology
Enzyme Activation
Enzyme Inhibitors: PD, pharmacology
*Fusion Proteins, bcr-abl: ME, metabolism
Genes, abl: GE, genetics
Interleukin-3: PD, pharmacology
Mice
*Microtubule-Associated Proteins: ME, metabolism
Morpholines: PD, pharmacology
Piperazines: PD, pharmacology
Promoter Regions (Genetics)
Protein Synthesis Inhibitors: PD, pharmacology
*Protein-Serine-Threonine Kinases
Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins c-akt
Pyrimidines: PD, pharmacology
RNA: ME, metabolism
Reverse Transcriptase Polymerase Chain Reaction
S Phase: DE, drug effects
Signal Transduction
Sirolimus: PD, pharmacology
Time Factors
Transfection
*Tumor Suppressor Proteins

RN 147604-94-2 (Cyclin-Dependent Kinase Inhibitor p27); 152459-95-5 (imatinib); 154447-36-6 (2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one); 53123-88-9 (Sirolimus); 564-25-0 (Doxycycline); 63231-63-0 (RNA); 66-81-9 (Cycloheximide)

CN 0 (Anti-Bacterial Agents); 0 (Cdkn1b protein, mouse); 0 (Cell Cycle Proteins); 0 (Chromones); 0 (Enzyme Inhibitors); 0 (Fusion Proteins, bcr-abl); 0 (Interleukin-3); 0 (Microtubule-Associated Proteins); 0 (Morpholines); 0 (Piperazines); 0 (Protein Synthesis Inhibitors); 0 (Proto-Oncogene Proteins); 0 (Pyrimidines); 0 (Tumor Suppressor Proteins); EC 2.7.1.137 (1-Phosphatidylinositol 3-Kinase); EC 2.7.1.37 (Protein-Serine-Threonine Kinases); EC 2.7.1.37 (Proto-Oncogene Proteins c-akt)

L66 ANSWER 27 OF 88 MEDLINE on STN
ACCESSION NUMBER: 1999262253 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10329492
TITLE: Crystallographic characterization of a stress-induced multifunctional protein, rat HBP-23.
AUTHOR: Hirotsu S; Abe Y; Nagahara N; Hori H; Nishino T; Okada K; Hakoshima T

CORPORATE SOURCE: Department of Molecular Biology, Nara Institute of Science and Technology (NAIST), 8916-5 Takayama, Nara, Ikoma, 630-01, Japan.
SOURCE: Journal of structural biology, (1999 Jun 1) Vol. 126, No. 1, pp. 80-3.
Journal code: 9011206. ISSN: 1047-8477.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jul 1999
Last Updated on STN: 14 Jul 1999
Entered Medline: 28 Jun 1999

AB HBP-23 is a stress-induced multifunctional rat protein that belongs to a novel family of antioxidant proteins, referred to as peroxiredoxins, and exhibits heme-binding and **inhibition** of c-**Abl** protein tyrosine **kinase**. Recombinant HBP-23 was crystallized by a hanging-drop vapor-diffusion method. The crystals belong to space group P41212 or P43212 with unit-cell dimensions of a = b = 73.47 A, c = 210.37 A and contain two protein molecules in the asymmetric unit. A data set at 2.7-A resolution was collected with a cryo-crystallographic technique. Crystals of selenomethionyl HBP-23 were also obtained under the same conditions.

CT Animals
Carrier Proteins: BI, biosynthesis
*Carrier Proteins: CH, chemistry
Carrier Proteins: IP, isolation & purification
Cloning, Molecular
Crystallization
Crystallography, X-Ray: MT, methods
Escherichia coli
Hemeproteins: BI, biosynthesis
*Hemeproteins: CH, chemistry
Hemeproteins: IP, isolation & purification
Rats
Recombinant Proteins: BI, biosynthesis
Recombinant Proteins: CH, chemistry
Recombinant Proteins: IP, isolation & purification
Research Support, Non-U.S. Gov't

CN 0 (Carrier Proteins); 0 (Hemeproteins); 0 (Recombinant Proteins); 0 (heme-binding protein)

L66 ANSWER 28 OF 88 MEDLINE on STN
ACCESSION NUMBER: 91341686 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1652014
TITLE: Sulfonylbenzoyl-nitrostyrenes: potential bisubstrate type inhibitors of the EGF-receptor tyrosine protein kinase.
AUTHOR: Traxler P M; Wacker O; Bach H L; Geissler J F; Kump W; Meyer T; Regenass U; Roesel J L; Lydon N
CORPORATE SOURCE: Oncology and Virology Research Department, Ciba-Geigy Ltd., Basel, Switzerland.
SOURCE: Journal of medicinal chemistry, (1991 Aug) Vol. 34, No. 8, pp. 2328-37.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109

ENTRY DATE: Entered STN: 13 Oct 1991
Last Updated on STN: 3 Mar 2000
Entered Medline: 25 Sep 1991

AB The synthesis and biological activities of a series of sulfonylbenzoyl-nitrostyrene derivatives, a novel class of selective bisubstrate type inhibitors of the EGF-receptor tyrosine protein kinase, are described. The most potent derivatives inhibited the EGF-R tyrosine kinase, using angiotensin II as exogenous substrate, with IC50 values of less than or equal to 1 microM. No **inhibition** of the v- **abl** tyrosine **kinase** or the serine/threonine kinases PKC and PK-A was observed. In addition, active derivatives (compounds 5 and 12) effectively blocked the autophosphorylation of the EGF-R in vitro. Starting from the acids 5, 7, and 9, a series of esters, amides, and peptides was synthesized with the aim of increasing cellular penetration. Amides 14-18 showed potent antiproliferative effects using the EGF-dependent Balb/MK mouse epidermal keratinocyte cell line. Additionally, with the amide 14 inhibition of EGF-R autophosphorylation was demonstrated in the A431 cell line. CAMM studies using a computer-generated model for the transition state of the gamma-phosphoryl transfer from ATP to a tyrosine moiety and fitting experiments using the highly potent derivative 7 (IC50 value = 54 nM) support the hypothesis that the sulfonylbenzoyl group mimics a diphosphate moiety in the transition state. These results demonstrate that the rational design of tyrosine kinase inhibitors, using the inhibitory nitrostyrene moiety as a tyrosine mimic together with the sulfonylbenzoyl moiety as a diphosphate mimic, leads to highly potent and selective multisubstrate type inhibitors.

CT Angiotensin II: ME, metabolism
Animals
Benzoates: CH, chemistry
***Benzoates: PD, pharmacology**
Cell Division: DE, drug effects
Cell Line
Chemistry
Computer Simulation
Crystallography
Enzyme Activation: DE, drug effects
Epidermal Growth Factor: PD, pharmacology
Keratinocytes: CY, cytology
Keratinocytes: DE, drug effects
Mice
Models, Molecular
Molecular Structure
Nitro Compounds: CH, chemistry
Nitro Compounds: PD, pharmacology
Phosphorylation
*Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Protein-Tyrosine Kinase: ME, metabolism
Receptor, Epidermal Growth Factor
Styrenes: CH, chemistry
*Styrenes: PD, pharmacology
Sulfones: CH, chemistry
*Sulfones: PD, pharmacology

RN 11128-99-7 (Angiotensin II); 62229-50-9 (Epidermal Growth Factor)

CN 0 (Benzoates); 0 (Nitro Compounds); 0 (Styrenes); 0 (Sulfones); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.112 (Receptor, Epidermal Growth Factor)

L66 ANSWER 29 OF 88 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4

ACCESSION NUMBER: 2005367387 EMBASE Full-text
TITLE: Imatinib in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia: Current

status and evolving concepts.

AUTHOR: Ottmann O.G.; Wassmann B.
CORPORATE SOURCE: Dr. O.G. Ottmann, Medizinische Klinik III, Abteilung fur Hamatologie und Onkologie, Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany. ottmann@em.uni-frankfurt.de
SOURCE: Best Practice and Research in Clinical Haematology, (2002) Vol. 15, No. 4, pp. 757-769. .
Refs: 51
ISSN: 1521-6926 CODEN: BPRCA5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Oct 2005
Last Updated on STN: 6 Oct 2005

AB Until recently, progress in the treatment of patients with Ph(+) acute lymphoblastic leukaemia (ALL) has been limited, and long-term survival, even with high-dose intensified chemotherapy, is rare. Allogeneic stem cell transplantation is potentially curative, but treatment-related mortality and rate of disease recurrence are substantial. With the advent of the ABL-selective tyrosine **kinase inhibitor** STI571 (imatinib mesylate, Glivec), it has become apparent that the understanding of crucial leukaemogenic pathways at the molecular level can lead to the development of specific and selective agents. In recent clinical trials, imatinib has demonstrated significant anti-leukaemic efficacy in patients with advanced Ph(+) ALL, in conjunction with a remarkably favourable safety profile. Clinical resistance to imatinib develops rapidly, highlighting the limitations of using imatinib as a single agent; however, the value of imatinib as an element of treatment has become apparent. Resistance mechanisms have already been identified that will enable the development of rational strategies to prevent or overcome resistance. On the basis of available clinical results, combinations of imatinib with established anti-leukaemic agents, as well as with novel, molecularly targeted treatment modalities, will need to be evaluated in advanced Ph(+) ALL. Incorporation of imatinib in the first-line treatment of de novo Ph(+) ALL and in the setting of minimal residual disease is a promising therapeutic approach which is currently being studied in clinical trials. Better understanding of targeted therapies, including strategies based on recruitment of host immune functions, as well as the prudent use of active chemotherapy agents, may eventually improve the outlook for patients with Ph(+) ALL. .COPYRGT. 2003 Elsevier Science Ltd. All rights reserved.

CT Medical Descriptors:
*acute lymphoblastic leukemia: DM, disease management
*acute lymphoblastic leukemia: DR, drug resistance
*acute lymphoblastic leukemia: DT, drug therapy
*acute lymphoblastic leukemia: ET, etiology
*acute lymphoblastic leukemia: RT, radiotherapy
*acute lymphoblastic leukemia: TH, therapy
Philadelphia chromosome positive cell
leukemogenesis
allogeneic stem cell transplantation
drug efficacy
enzyme activity
cell proliferation
chromosome translocation

drug mechanism
cancer relapse: DT, drug therapy
cancer relapse: PC, prevention
drug safety
drug dose regimen
cancer survival
blood toxicity: SI, side effect
neutropenia: SI, side effect
thrombocytopenia: SI, side effect
gastrointestinal symptom: SI, side effect
peripheral edema: SI, side effect
face edema: SI, side effect
muscle cramp: SI, side effect
salvage therapy
cancer risk
skull irradiation
drug tolerability
drug absorption
drug blood level
central nervous system disease: DT, drug therapy
central nervous system disease: PC, prevention
nausea: SI, side effect
diarrhea: SI, side effect
rash: SI, side effect
headache: SI, side effect
infection: SI, side effect
bleeding: SI, side effect
drug protein binding
minimal residual disease: DI, diagnosis
drug metabolism
drug potentiation
drug antagonism
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*imatinib: AE, adverse drug reaction
*imatinib: CT, clinical trial
*imatinib: CR, drug concentration
*imatinib: DO, drug dose
*imatinib: IT, drug interaction
*imatinib: DT, drug therapy
*imatinib: PO, oral drug administration
*imatinib: PK, pharmacokinetics
*imatinib: PD, pharmacology
BCR ABL protein: EC, endogenous compound
orosomucoid: EC, endogenous compound
multidrug resistance protein 1: EC, endogenous compound
simvastatin: IT, drug interaction
cyclosporin A: IT, drug interaction
antifungal agent: IT, drug interaction
antiinfective agent: IT, drug interaction

RN (imatinib) 152459-95-5, 220127-57-1; (orosomucoid) 79921-18-9; (simvastatin) 79902-63-9; (cyclosporin A) 59865-13-3, 63798-73-2

CN Sti 571; Glivec

L66 ANSWER 30 OF 88 EMBASE

ACCESSION NUMBER: 2006203437 EMBASE Full-text
TITLE: Smallpox antiviral drug development: Satisfying the animal efficacy rule.
AUTHOR: Jordan R.; Hruby D.
CORPORATE SOURCE: Dr. R. Jordan, SIGA Technologies Inc., 4575 SW Research Way, Corvallis, OR 97333, United States. rjordan@sgph.com
SOURCE: Expert Review of Anti-Infective Therapy, (2006) Vol. 4, No. 2, pp. 277-289. .
Refs: 63
ISSN: 1478-7210 E-ISSN: 1744-8336 CODEN: ERATCK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 2006
Last Updated on STN: 18 May 2006

AB Concerns over the potential use of variola virus as a biological weapon have prompted new interest in the development of small molecule therapeutics to prevent and treat smallpox infection. Since smallpox is no longer endemic, human clinical trials designed to link antiviral efficacy to clinical outcome have been supplanted by antiviral efficacy evaluations in animal models of orthopoxvirus disease. This poses a unique challenge for drug development; how can animal efficacy data with a surrogate virus be used to establish clinical correlates predictive of human disease outcome? This review will examine the properties of selected animal models that are being used to evaluate poxvirus antivrial drug candidates, and discuss how data from these models can be used to link drug efficacy to clinical correlates of human disease. .COPYRGT. 2006 Future Drugs Ltd.

CT Medical Descriptors:
*smallpox: DT, drug therapy
*smallpox: ET, etiology
*smallpox: PC, prevention
Smallpox virus
drug efficacy
biological warfare
methodology
treatment outcome
disease model
Orthopoxvirus
correlation analysis
prediction
virus replication
Vaccinia virus
Monkeypox virus
Cowpox virus
disease course
immune response
food and drug administration
drug approval
enzyme inhibition
inhibition kinetics
experimentation
antiviral activity
inoculation
Ectromelia virus

rabbit
primate
virus transmission
human
nonhuman
mouse
clinical trial
review

CT Drug Descriptors:
***antivirus agent: CT, clinical trial**
***antivirus agent: DV, drug development**
***antivirus agent: DT, drug therapy**
***antivirus agent: PD, pharmacology**
smallpox vaccine: DT, drug therapy
cidofovir: DT, drug therapy
cidofovir: PD, pharmacology
DNA polymerase: EC, endogenous compound
imatinib: DT, drug therapy
imatinib: PD, pharmacology
n [4 (3 chloro 4 fluoroanilino) 7 (3 morpholinopropoxy) 6 quinazolinyl]acrylamide: DT, drug therapy
n [4 (3 chloro 4 fluoroanilino) 7 (3 morpholinopropoxy) 6 quinazolinyl]acrylamide: PD, pharmacology
Abelson kinase: EC, endogenous compound
antiinfective agent: DT, drug therapy
antiinfective agent: PD, pharmacology
st 246: DT, drug therapy
st 246: PD, pharmacology
virus protein: EC, endogenous compound
cytokine: EC, endogenous compound
unclassified drug

RN (cidofovir) 113852-37-2; (DNA polymerase) 37217-33-7; (imatinib) 152459-95-5, 220127-57-1; (n [4 (3 chloro 4 fluoroanilino) 7 (3 morpholinopropoxy) 6 quinazolinyl]acrylamide) 267243-28-7, 338796-35-3

CN Vistide; Gleevec; Ci 1033; St 246

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ACCESSION NUMBER: 2005329592 EMBASE Full-text
TITLE: Gleevec casts a pox on poxviruses.
AUTHOR: McFadden G.
CORPORATE SOURCE: G. McFadden, University of Western Ontario, Robarts Research Institute, London, Ont. N6G 2V4, Canada. mcfadden@robarts.ca
SOURCE: Nature Medicine, (2005) Vol. 11, No. 7, pp. 711-712. .
Refs: 12
ISSN: 1078-8956 CODEN: NAMEFI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 004 Microbiology
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Aug 2005
Last Updated on STN: 11 Aug 2005

CT Medical Descriptors:
*Poxvirus infection: DT, drug therapy
*chronic myeloid leukemia: DT, drug therapy
Poxvirus

virus morphogenesis
cytoplasm
virion
drug efficacy
drug inhibition
cell culture
antiviral activity
food and drug administration
drug marketing
virus replication
vaccinia
monkeypox
human
nonhuman
short survey
priority journal
Drug Descriptors:
*imatinib: IT, drug interaction
*imatinib: DT, drug therapy
*imatinib: PD, pharmacology
*cidofovir: DT, drug therapy
*cidofovir: PD, pharmacology
protein tyrosine kinase inhibitor: DT, drug therapy
antivirus agent: DT, drug therapy
antivirus agent: PD, pharmacology
Abelson kinase: IT, drug interaction
protein tyrosine kinase: IT, drug interaction
u 1026: PD, pharmacology
mitogen activated protein kinase inhibitor: PD, pharmacology
n [4 (3 chloro 4 fluoroanilino) 7 (3 morpholinopropoxy) 6 quinazolinyl]acrylamide: PD, pharmacology
unclassified drug
RN (imatinib) 152459-95-5, 220127-57-1; (cidofovir) 113852-37-2; (protein tyrosine kinase) 80449-02-1; (n [4 (3 chloro 4 fluoroanilino) 7 (3 morpholinopropoxy) 6 quinazolinyl]acrylamide) 267243-28-7, 338796-35-3
CN Gleevec; U 1026; Ci 1033

L66 ANSWER 32 OF 88 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005241126 EMBASE Full-text
TITLE: Gastric GI Stromal Tumors (GISTs): The role of surgery in the era of targeted therapy.
AUTHOR: Heinrich M.C.; Corless C.L.
CORPORATE SOURCE: Dr. M.C. Heinrich, R and D-19 3710, SW, US Veterans Hospital Road, Portlands, OR 97239. heinrich@ohsu.edu
SOURCE: Journal of Surgical Oncology, (1 Jun 2005) Vol. 90, No. 3, pp. 195-207. .
Refs: 148
ISSN: 0022-4790 CODEN: JSONAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 009 Surgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005

AB Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm arising in the stomach. These tumors were previously classified as smooth muscle tumors, but in recent years it has become clear that they are clinically, pathologically, and molecularly distinct from other tumors and are much more common than previously appreciated. Historically, patients with primary localized or advanced GIST have been managed surgically, as there was no proven role of other treatment modalities such as radiation or chemotherapy. However, the field of GIST was revolutionized with the 1998 discovery that the vast majority of these tumors have oncogenic gain-of-function mutations of the KIT receptor tyrosine kinase. Follow-up studies have confirmed that KIT is both a useful diagnostic marker and an excellent therapeutic target. Imatinib, an **inhibitor** of KIT kinase activity, is now the standard front-line therapy for patients with advanced GIST. In this review, we discuss pathological and molecular features of gastric GISTs and review the historic and current roles of surgery in the treatment of patients with primary or metastatic GIST. The importance of a multi-disciplinary approach using both surgery and imatinib therapy is emphasized. .COPYRGT. 2005 Wiley-Liss, Inc.

CT Medical Descriptors:
*gastrointestinal stromal tumor: DM, disease management
*gastrointestinal stromal tumor: DR, drug resistance
*gastrointestinal stromal tumor: DT, drug therapy
*gastrointestinal stromal tumor: SU, surgery
muscle tumor
chemotherapy
follow up
drug activity
metastasis
clinical feature
incidence
gene mutation
exon
prognosis
mitosis index
preoperative evaluation
bleeding: CO, complication
liver metastasis: CO, complication
quality of life
cancer risk
human
clinical trial
conference paper
priority journal
Drug Descriptors:
*protein tyrosine kinase: DT, drug therapy
*protein tyrosine kinase: PD, pharmacology
*imatinib: CT, clinical trial
*imatinib: DO, drug dose
*imatinib: DT, drug therapy
*imatinib: PD, pharmacology
antiinfective agent: DT, drug therapy
stem cell factor receptor: PD, pharmacology
protein bcl 2: PD, pharmacology
CD34 antigen: CB, drug combination
CD34 antigen: PD, pharmacology
alpha actin: PD, pharmacology
desmin: CB, drug combination
desmin: PD, pharmacology
platelet derived growth factor: PD, pharmacology
Abelson kinase: EC, endogenous compound

5 (5 fluoro 1,2 dihydro 2 oxo 3 indolylidenemethyl) 2,4 dimethyl 1h pyrrole 3 carboxylic acid (2 diethylaminoethyl)amide: CT, clinical trial
5 (5 fluoro 1,2 dihydro 2 oxo 3 indolylidenemethyl) 2,4 dimethyl 1h pyrrole 3 carboxylic acid (2 diethylaminoethyl)amide: DT, drug therapy placebo

RN (protein tyrosine kinase) 80449-02-1; (imatinib) 152459-95-5, 220127-57-1; (protein bcl 2) 219306-68-0; (5 (5 fluoro 1,2 dihydro 2 oxo 3 indolylidenemethyl) 2,4 dimethyl 1h pyrrole 3 carboxylic acid (2 diethylaminoethyl)amide) 557795-19-4

CN (1) Gleevec

CO (1) Novartis

L66 ANSWER 33 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 5

ACCESSION NUMBER: 2001:436182 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100436182
TITLE: Novel reduced benzo(j)fluoranthen-3-ones from Cladosporium cf. cladosporioides with cytokine production and tyrosine kinase inhibitory properties.
AUTHOR(S): Wrigley, Stephen K. [Reprint author]; Ainsworth, A. Martyn; Kau, David A.; Martin, Steven M.; Bahl, Sangeeta; Tang, Jenny S.; Hardick, David J.; Rawlins, Philip; Sadheghi, Roya; Moore, Michael
CORPORATE SOURCE: Cubist Pharmaceuticals (UK) Limited, 545 Ipswich Road, Slough, SL1 4EQ, UK
swrigley@cubist.com
SOURCE: Journal of Antibiotics (Tokyo), (June, 2001) Vol. 54, No. 6, pp. 479-488. print.
CODEN: JANTAJ. ISSN: 0021-8820.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 2001
Last Updated on STN: 22 Feb 2002

AB A series of reduced benzo(j)fluoranthen-3-ones (1apprx4) was isolated from fermentations of a fungal strain CBUK20700 (CBS 100220), classified as Cladosporium cf. cladosporioides, during a **microbial** extract screening programme to identify inhibitors of anti-CD28-induced interleukin-2 (IL-2) production by Jurkat E6-1 cells as potential immunosuppressive agents. These compounds were also found to be tyrosine kinase inhibitors. The structures of compounds 1apprx4 were elucidated by spectroscopic methods including the HMQC, HMBC and NOESY NMR experiments. The most potent compound in the series, (6bS,7R,8S)-7-methoxy-4,8,9- trihydroxy-1,6b,7,8-tetrahydro-2H-benzo(j)fluoranthen-3-one (1) inhibited anti-CD28-induced IL-2 production and Abl tyrosine kinase with IC50 values of 400 and 60 nM respectively. The 6b-stereoisomeric 2 was a moderate inhibitor of both IL-2 production and Abl tyrosine kinase while the 8-oxo derivative 3 was inactive in both assays. The 8-O-methyl ether 4 was a moderate inhibitor of IL-2 production but exhibited potent **inhibition** of **Abl** tyrosine **kinase** with an IC50 of 45 nM.

CC Cytology - Human 02508
Pharmacognosy and pharmaceutical botany 54000

IT Major Concepts
Pharmacognosy (Pharmacology)

IT Chemicals & Biochemicals
(6bS,7R,8S)-7-methoxy-4,8,9-trihydroxy-1,6b,7,8-tetrahydro-2H-benzo[j]fluoranthen-3-one: immunosuppressant-drug; 8-O-methyl ether; Abl tyrosine kinase; anti-CD28-induced interleukin-2 [anti-CD28-induced IL-2]: production; benzo[j]fluoranthen-3-ones: immunosuppressant-drug

IT Methods & Equipment
HMBC [heteronuclear multiple-bond correlation]: analytical method; HMQC [heteronuclear multiple quantum correlation spectroscopy]: analytical

method; NOE [nuclear Overhauser effect spectroscopy]; NMR [nuclear Overhauser effect spectroscopy]:
analytical method
IT Miscellaneous Descriptors
microbial extract screening program
ORGN Classifier
Fungi 15000
Super Taxa
Plantae
Organism Name
Cladosporium cf. cladosporioides: strain-CBUK20700
Taxa Notes
Fungi, Microorganisms, Nonvascular Plants, Plants
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Jurkat E6-1 cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L66 ANSWER 34 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 6
ACCESSION NUMBER: 2001:294257 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100294257
TITLE: Clinical activity of an ABL-tyrosine **kinase inhibitor** (STI571) in a patient with CML lymphoid blast crisis relapsing after allogeneic stem cell transplantation.
AUTHOR(S): Wassmann, B. [Reprint author]; Scheuring, U.; Thiede, Ch.; Bornhaeuser, M.; Griesinger, F.; Petershofen, E.; Gschaidmeier, H.; Capdeville, R.; Hoelzer, D.; Ottmann, O. G.
CORPORATE SOURCE: Dept. of Hematology, University of Frankfurt, Frankfurt, Germany
SOURCE: Blood, (**November 16, 2000**) Vol. 96, No. 11 Part 2, pp. 218b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002
AB A 25-yr.-old male with Ph-pos. CML and early onset lymphoid blast crisis relapsing after a 2nd non-myeloablative allogeneic, HLA-identical sibling PBSCT despite grade III GvHD (gut, skin) was referred to our hospital for treatment with the ABL-tyrosine **kinase inhibitor** STI571 within a multicenter phase II clinical trial (STI109) in October 1999. Previous phase I clinical trials of STI571 have shown remarkable activity in chronic phase CML, blast crisis and Ph+ acute lymphocytic leukemia (ALL) (Druker et al ASH: 368a, 697a,1999). The patients medical history included a 7-month iv. drug abuse, acute hepatitis B infection 2 yrs. prior to diagnosis of CML and ongoing methadone substitution. Baseline cytogenetics revealed complex aberrant karyotype including t(9;22) in 83% of metaphases, bone marrow analysis showed marked hypercellularity and accelerated phase of CML, donor chimerism had dropped to 76%. STI571 therapy was initiated at a single daily dose of 400 mg p.o.. GvHD prophylaxis with steroids 60mg/d was tapered and discontinued

after 3 months without recurrence of GVHD. After 4 wks. treatment marrow, after 3 mon cytology normalized, a complete cytogenetic response and an increase in donor chimerism to 94% at 4 wks. and to >99% at 9 wks. occurred. BCR-ABL expression as measured by real time quantitative PCR showed a decrease by more than 2 logs after 4 wks. of STI571 treatment and remained negative since 8 wks. after starting treatment. The negative values reflect an overall reduction of BCR-ABL expression by more than 4 logs. Complete cytogenetic and molecular remission and stable donor chimerism are maintained after 9 mts. of treatment. STI571 was well tolerated, treatment related side effects were limited to reversible grade II neutropenia and grade I nausea not requiring pharmacologic intervention. Reactivation of hepatitis B after 7 mts. of treatment with rapid increase in liver enzymes necessitated short-term interruption of therapy and initiation of **antiviral** therapy. The pronounced clinical efficacy of STI571 as seen in this pt. demonstrates that STI571 is a promising therapeutic option in patients with BCR-ABL positive leukemias who have failed allogeneic bone marrow transplantation. Our findings provide the rationale for a novel treatment strategy employing STI 571 subsequent to allogeneic bone marrow transplantation.

CC Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
General biology - Symposia, transactions and proceedings 00520
Anatomy and Histology - Surgery 11105
Pathology - Therapy 12512
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)

IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Myeloid, Chronic (MeSH)

IT Diseases
graft-vs-host disease: immune system disease
Graft vs Host Disease (MeSH)

IT Chemicals & Biochemicals
ABL-tyrosine kinase inhibitor: clinical activity

IT Methods & Equipment
allogeneic stem cell transplantation: surgical method, therapeutic method

IT Miscellaneous Descriptors
chronic myeloid leukemia lymphoid blast crisis; Meeting Abstract

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L66 ANSWER 35 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 7

ACCESSION NUMBER: 1992:525930 BIOSIS Full-text
DOCUMENT NUMBER: PREV199294134005; BA94:134005
TITLE: EFFECT OF HERBIMYCIN A AN **ANTAGONIST** OF TYROSINE **KINASE** ON BCR-ABL ONCOPROTEIN-ASSOCIATED

TI [illegible] PROLIFERATIONS ABROGATIVE EFFECT ON THE TRANSFORMATION OF MURINE HEMATOPOIETIC CELLS BY TRANSFECTION OF A RETROVIRAL VECTOR EXPRESSING ONCOPROTEIN P210BCR-ABL AND PREFERENTIAL INHIBITION ON PH-1-POSITIVE LEUKEMIA CELL GROWTH.

AUTHOR(S): OKABE M [Reprint author]; UEHARA Y; MIYAGISHIMA T; ITAYA T; TANAKA M; KUNI-EDA Y; KUROSAWA M; MIYAZAKI T

CORPORATE SOURCE: THIRD DEP INTERNAL MED, HOKKAIDO UNIVERSITY SCH MED, KITA-15, NISHI-7, KITA-KU,, SAPPORO 060, JPN

SOURCE: Blood, (1992) Vol. 80, No. 5, pp. 1330-1338.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Nov 1992
Last Updated on STN: 20 Nov 1992

AB Herbimycin A, a benzoquinoid ansamycin antibiotic, was demonstrated to decrease intracellular phosphorylation by protein tyrosine kinase (PTK). In Philadelphia chromosome (Ph1)-positive leukemias such as chronic myelogenous leukemia (CML) and Ph1-positive acute lymphoblastic leukemia (ALL), both of which express bcr-abl fused gene products (P210bcr-abl or P190bcr-abl protein kinase) with augmented tyrosine kinase activities, herbimycin A markedly inhibited the in vitro growth of the Ph1-positive ALL cells and the leukemic cells derived from CML blast criteria. However, the same dose of herbimycin A did not inhibit in vitro growth of a broad spectrum of Ph1-negative human lekemia cells, and several other protein kinase antagonists also displayed no preferential inhibition. Furthermore, we demonstrated that herbimycin A has a antagonizing effect on the growth of transformed cells by a transfection of retroviral amphotrophic vector expressing P210bcr/abl into a murine leukemia (IL)-3-dependent myeloid FDC-P2 cell line. This inhibition was abrogated by the addition of sulfhydryl compounds, similar to the reaction previously described for Rous sarcoma **virus** transformation. The inhibitory effect of herbimycin A on the growth of Ph1-positive cells was associated with decreased bcr/abl tyrosine kinase activity, but no decrease of bcr-abl mRNA and protein, suggesting that the inactivation of bcr-abl tyrosine kinase activity by herbimycin A may be induced by its binding to the bcr-abl protein portion that is rich with sulfhydryl groups. The present study indicates that herbimycin A is a beneficial agent for the investigation of the role of the bcr-abl gene in Ph1-positive leukemias and further suggests that the development of agents inhibiting the bcr-abl gene product may offer a new therapeutic potential or Ph1-positive leukemias.

CC Genetics - Animal 03506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Clinical pharmacology 22005
Pharmacology - Blood and hematopoietic agents 22008
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Virology - Animal host viruses 33506
Medical and clinical microbiology - Virology 36006
Chemotherapy - Antiviral agents 38506

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Genetics; Infection; Pharmacology; Tumor Biology

IT Miscellaneous Descriptors
ROUS SARCOMA **VIRUS** ONCORNAVIRUS **ANTIVIRAL-DRUG**

ANTINEOPLASTIC-DRUG ACUTE LYMPHOBLASTIC-LEUKEMIA-PHILADELPHIA CHROMOSOME-POSITIVE LEUKEMIA CHRONIC MYELOGENOUS LEUKEMIA POSSIBLE THERAPY
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 70563-58-5 (HERBIMYCIN A)

L66 ANSWER 36 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:298331 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200298331
TITLE: Modulation of p210BCR-ABL activity in transduced primary human hematopoietic cells controls lineage programming.
AUTHOR(S): Chalandon, Yves; Jiang, Xiaoyan; Hazlewood, Glen; Loutet, Slade; Conneally, Eibhlin; Eaves, Allen; Eaves, Connie [Reprint author]
CORPORATE SOURCE: Terry Fox Laboratory, 601 W 10th Ave, Vancouver, BC, V5Z 1L3, Canada
ceaves@bccancer.bc.ca
SOURCE: Blood, (May 1, 2002) Vol. 99, No. 9, pp. 3197-3204. print.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 May 2002
Last Updated on STN: 22 May 2002

AB Retroviral transduction of primary hematopoietic cells with human oncogenes provides a powerful approach to investigating the molecular mechanisms controlling the normal proliferation and differentiation of these cells. Here we show that primitive human CD34+ cord blood cells, including multipotent as well as granulopoietic- and erythroid-restricted progenitors, can be efficiently transduced with a MSCV-BCR-ABL-IRES-GFP retrovirus, resulting in the sustained expression by their progeny of very high levels of tyrosine phosphorylated p210BCR-ABL. Interestingly, even in the presence of growth factors that supported the exclusive production of granulopoietic cells from green fluorescent protein (GFP)-transduced control cells, BCR-ABL-transduced progenitor subpopulations generated large numbers of erythropoietin-independent terminally differentiating erythroid cells and reduced numbers of granulopoietic cells. Analyses of individual clones generated by single transduced cells in both semisolid and liquid cultures showed this BCR-ABL-induced erythroid differentiation response to be elicited at a high frequency from all types of transduced CD34+ cells independent of their apparent prior lineage commitment status. Additional experiments showed that this erythroid differentiation response was largely prevented when the cells were transduced and maintained in the presence of the BCR-ABL-specific tyrosine kinase inhibitor, STI-571. These findings indicate that overexpression of BCR-ABL in primary human hematopoietic cells can activate an erythroid differentiation

program in apparently granulopoietic-restricted cells through a BCR-ABL kinase-dependent mechanism, thus providing a new molecular tool for elucidating mechanisms underlying lineage fate determination in human hematopoietic cells and infidelity in human leukemia.

CC Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Genetics of bacteria and viruses 31500
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology

IT Parts, Structures, & Systems of Organisms
CD34-positive cord blood cell: immune system; hematopoietic cell: blood and lymphatics, differentiation, proliferation

IT Diseases
leukemia: blood and lymphatic disease, neoplastic disease
Leukemia (MeSH)

IT Chemicals & Biochemicals
STI-571: enzyme inhibitor-drug; p210-BCR-ABL; tyrosine kinase

IT Miscellaneous Descriptors
cell lineage programming; retroviral transduction

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
retrovirus
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 152459-95-5 (STI-571)
80449-02-1 (tyrosine kinase)

GEN human BCR-ABL oncogene (Hominidae)

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ACCESSION NUMBER: 2003:47357 BIOSIS Full-text

DOCUMENT NUMBER: PREV200300047357
TITLE: Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia.
AUTHOR(S): Schwarz, Michaela; Kreuzer, Karl-Anton [Reprint Author]; Baskaynak, Goekben; Doerken, Bernd; le Coutre, Philipp
CORPORATE SOURCE: Medizinische Klinik M.S. Haematologie und Onkologie, Universitaetsklinikum Charite, Humboldt-Universitaet zu Berlin, Augustenburger Platz 1, Campus Virchow-Klinikum, 13353, Berlin, Germany
karl-anton.kreuzer@charite.de
SOURCE: European Journal of Haematology, (October 2002)
Vol. 69, No. 4, pp. 254-256. print.
ISSN: 0902-4441 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003

AB Imatinib mesylate **blocks** bcr/**abl kinase** activity effectively, and thus is a promising drug in Philadelphia chromosome positive leukemias. While under imatinib treatment high hematological and cytogenetic response rates could be observed, usually only mild non-hematological side-effects like skin rash, edema, and muscular cramps occur. Here we report two severe cases of acute generalized exanthematous pustulosis due to imatinib. In both patients the generalized pustular eruptions could be observed 12 wk after initiation of imatinib treatment. Numerous **microbiological** investigations excluded an infectious etiology, and histopathology of cutaneous lesions was consistent with acute generalized exanthematous pustulosis. Accordingly, withdrawal of imatinib led to a restitutio at integrum of the integument. Our report confirms another single observation of acute generalized exanthematous pustulosis in chronic myeloid leukemia under imatinib therapy, and confirms that this is a rare but proven adverse effect of imatinib.

CC Cytology - Animal 02506
Cytology - Human 02508
Pathology - Therapy 12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Integumentary system - Pathology 18506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Toxicology - General and methods 22501
Toxicology - Pharmacology 22504
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Dermatology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Parts, Structures, & Systems of Organisms
Philadelphia chromosome

IT Diseases
acute generalized exanthematous pustulosis: integumentary system disease, toxicity, drug-induced, etiology

IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease, complications, drug therapy
Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
imatinib mesylate: antineoplastic-drug, toxicity

ORGN Classifier
Hominidae 86215

Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): adult, middle age, Caucasian, patient, female
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 220127-57-1 (imatinib mesylate)

L66 ANSWER 38 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:367836 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300367836
TITLE: Pro-Apoptotic Protein Bax Is Involved in the Development of B-Cell Acute Lymphoblastic Leukemia Induced by BCR/ABL Oncogene in Mice.
AUTHOR(S): Li, Shaoguang [Reprint Author]; Hu, Yiguo [Reprint Author]
CORPORATE SOURCE: Research, The Jackson Laboratory, Bar Harbor, ME, USA
SOURCE: Blood, (**November 16 2002**) Vol. 100, No. 11, pp.
Abstract No. 4352. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003

AB Human Philadelphia chromosome-positive (Ph+) leukemia induced by the BCR/ABL oncogene is a hematopoietic stem cell malignant disease that arises from a reciprocal translocation between chromosome 22 and 9. This disease includes chronic myeloid leukemia (CML) and B-cell acute lymphoblastic leukemia (B-ALL). The **ABL** tyrosine **kinase inhibitor** STI 571 (Gleevec) has been shown to induce complete hematologic response in all interferon-resistant chronic phase CML patients. However, observations that STI 571 induced cellular and clinical drug resistance have raised a possibility that use of STI 571 as a single agent may not prevent eventual disease progression to terminal blast crisis. Moreover, it has been shown that STI 571 is much less effective in treating CML blast crisis patients and patients with Ph+ B-ALL. Identification of new therapeutic targets will help improve available therapeutic methods. We focus on the determination of signaling pathways utilized by BCR/ABL to induce Ph+ leukemias. We tested in vivo the role of the pro-apoptotic protein Bax, a Bcl-2 family member, in the induction of B-ALL by BCR/ABL in our bone marrow transduction/transplatation mouse model. Non-5-FU treated bone marrow cells from homozygous Bax gene knock out mice (Bax-/-) were transduced with P210 BCR/ABL retrovirus followed by transplantation into wild type recipient mice. For control, wild type bone marrow cells transduced with the same **virus** were transplanted into wild type recipient mice. We found that in the absence of Bax (Bax-/-) the disease developed much rapidly compared to wild type control. In the absence of Bax, all the mice developed B-ALL and died within 38 days post bone marrow transplantation. These mice showed infiltration of CD19/B220-positive B leukemic cells in the spleen, liver and bone marrow, and accumulation of the leukemic cells in pleural effusion. All the control mice also developed B-ALL, and died within 56 days post bone marrow transplantation. Strikingly, we observed that in some mice Bax deficiency promoted the growth of myeloid (Gr-1+) leukemic cells, whose accumulation in the spleen has never been observed when wild type mice were used in our B-ALL mouse model system. The detailed nature of these BCR/ABL-expressing myeloid cells is under the investigation.

Taken together, our findings suggest that the functional deregulation of the pro-apoptotic protein Bax accelerates the development of B-ALL induced by BCR/ABL and promotes progression of the disease.

CC General biology - Symposia, transactions and proceedings 00520
Genetics - General 03502
Genetics - Animal 03506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Pathology - Therapy 12512
Digestive system - Physiology and biochemistry 14004
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Respiratory system - Pathology 16006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Molecular Genetics (Biochemistry and Molecular Biophysics); Tumor Biology

IT Parts, Structures, & Systems of Organisms
bone marrow: blood and lymphatics, immune system; liver: digestive system; spleen: blood and lymphatics, immune system

IT Diseases
B-cell acute lymphoblastic leukemia: blood and lymphatic disease, immune system disease, neoplastic disease, genetics
Leukemia, B-Cell, Acute (MeSH)

IT Diseases
pleural effusion: respiratory system disease
Pleural Effusion (MeSH)

IT Chemicals & Biochemicals
5-FU [5-fluorouracil]: antineoplastic-drug; Bax: pro-apoptotic protein; STI 571 [Gleevec]: antineoplastic-drug

IT Methods & Equipment
bone marrow transplantation: laboratory techniques

IT Miscellaneous Descriptors
disease progression

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 51-21-8 (5-FU)
51-21-8 (5-fluorouracil)
152459-95-5 (STI 571)
152459-95-5 (Gleevec)

GEN mouse BCR/ABL gene (Muridae); mouse Bax gene (Muridae)

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ACCESSION NUMBER: 2003:335834 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300335834
TITLE: Identification of Small Molecule Inhibitors of BCR/ABL Tyrosine Kinase through

...ructure Based Virtual Screening.

AUTHOR(S): Peng, Hui [Reprint Author]; Qi, Jing [Reprint Author], Huang, Niu [Reprint Author]; Yang, Chunzheng [Reprint Author]; Wang, Jiangxiang [Reprint Author]

CORPORATE SOURCE: State Key Laboratory of Experimental Hematology, Institute of Hematology, CAMSandPUMC, Tianjin, China

SOURCE: Blood, (**November 16 2002**) Vol. 100, No. 11, pp. Abstract No. 1234. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

AB Over 90% of chronic myelogenous leukemia (CML) and 10% to 25% of adult acute lymphoblastic leukemia (ALL) are associated with a reciprocal translocation between chromosomes 9 and 22 that produces a Bcr-Abl fusion gene. Since transformation by BCR/ABL is absolutely dependent on tyrosine kinase activity, it has been evident that BCR/ABL tyrosine kinase domain could be an attractive target for drug development. Herein, we describe the discovery of novel classes of small molecule inhibitors targeted at the catalytic domains of Abl tyrosine kinase, in which a centrally located "activation loop" is not phosphorylated, by computational 3-D database search. A preliminary DOCK screening against the distinctive inactive conformation of the catalytic domain of BCR/ABL was performed on a smaller 3D database that 202,657 commercially available organic compounds had been built via in-house procedures. 20,000 top compounds with steric complementarity to the binding site was selected for rigorous secondary DOCK screening. The docked complex geometries was used for rescoring by other representively scoring functions. 1000 compounds with a high potential to have high scores by different scoring functions was selected for further diversity analysis. From different structurally diverse clusters, 15 compounds were selected for biological assay based on physico-chemical properties, chemical stability, potential toxicity and potential metabolism. Nine of the 15 showed inhibitory activity against Ph+ human K562 cells with IC50 value ranging from 0.4 to 100 mug/ml. Analysis of the computer-generated binding modes showed that the active compounds interacted nicely with inactive conformation of the activation loop in the down-regulated form of ABL tyrosine kinase. The structural details and the unique binding motif may contribute to the future development of BCR/**ABL** tyrosine **kinase inhibitors.**

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Pathology - General 12502
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology; Tumor

Biology
IT Parts, Structures, & Systems of Organisms
Philadelphia chromosome
IT Diseases
acute lymphoblastic leukemia: blood and lymphatic disease, neoplastic disease, genetics
Leukemia, Lymphocytic, Acute (MeSH)
IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, neoplastic disease, genetics, pathology
Leukemia, Myeloid, Chronic (MeSH)
IT Chemicals & Biochemicals
Abl tyrosine kinase [EC 2.7.1.112]; BCR/ABL tyrosine kinase
IT Methods & Equipment
structure based virtual screening: imaging and microscopy techniques, laboratory techniques
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
K562 cell line (cell line): human leukemia cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 98037-52-6 (Abl tyrosine kinase)
80449-02-1 (Abl tyrosine kinase)
98037-52-6 (EC 2.7.1.112)
80449-02-1 (EC 2.7.1.112)
138238-67-2 (BCR/ABL tyrosine kinase)

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ACCESSION NUMBER: 2003:368309 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300368309
TITLE: Decreasing BCR-ABL Level in Contrast to the BCR-ABL Load at the Start of Treatment, Is Significantly Associated with the Cytogenetic Response to Imatinib in Chronic Myelogenous Leukemia Patients.
AUTHOR(S): Colombat, Marie [Reprint Author]; Chollet, Claudine [Reprint Author]; Fort, Marie-Pierre [Reprint Author]; Barthe, Christophe [Reprint Author]; Leguay, Thibaut [Reprint Author]; Bilhou-Nabera, Chrystele [Reprint Author]; Reiffers, Josy [Reprint Author]; Marit, Gerald [Reprint Author]; Mahon, Francois-Xavier [Reprint Author]
CORPORATE SOURCE: Laboratoire Greffe de Moelle UMR CNRS 5540, Universite Victor Segalen, Bordeaux, France
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 4826. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003
AB The causative event in the initiation of chronic myeloid leukemia (CML) is the formation of the BCR-ABL oncogene, molecular counterpart of Philadelphia

chromosome (Ph), which codes for a constitutively active Bcr-Abl tyrosine kinase. Imatinib mesylate formerly STI-571 **inhibits** the Bcr-Abl tyrosine **kinase** with high selectivity has been demonstrated to induce clinical and cytogenetic responses in patients(pts) with CML. Here we report the quantitative real time PCR (QRT-PCR) data for 47 patients (median age 55 years (range 21 - 81)) with CML in chronic phase treated with imatinib mesylate previously resistant to Interferon alpha. Among these 47 patients, 26 achieved a complete cytogenetic remission (CCR) i.e. 0% of Ph positive cells, after treatment with STI571. First we studied and followed the minimum residual disease (MRD) of these 26 CCR patients. Triplicate QRT-PCR analyses were performed on blood specimens using ABL transcripts as the endogenous control and the result reported as BCR-ABL/ABL percentage ratio. BCR-ABL transcripts were detected by QRT-PCR in 26 patients with a median BCR-ABL/ABL ratio of 0.2% (range - negative to 9.8), mean value 0.86%. In 6 patients the BCR-ABL/ABL ratio was< 0.001% after a follow up of at least 9 months. Three pts revealed an increase in BCR-ABL/ABL ratio during the follow up which was correlated with cytogenetic relapse. The BCR-ABL/ABL ratio was <1.0% in 22 CCR pts. In 4 pts the ratio was > 1% despite the fact that the Ph chromosome could not be detected in marrow metaphases. In most of cases the QRT-PCR data identified those patients who had achieved CCR before the cytogenetic data were available. For 31 patients the BCR-ABL/ABL ratio was also determined just before starting imatinib and a wide variation of BCR-ABL/ABL ratio was observed with a median value of 38.2 % (range which was not significantly associated with CCR achievement. Indeed, the probability to achieve CCR at 6 months for the 16 patients with a ratio> 38.2 was 31+-23% vs 47+-26 for the other patients (p=0.66). In addition, the ratio of BCR-ABL/ABL%/Ph+% corresponding indirectly to the quantity of Bcr-Abl mRNA by leukemic cells was not statistically significant for predicting cytogenetic response (p=0.49). The degree and duration of molecular response achieved with STI571 therapy is currently unknown but may have prognostic significance. As compare to the HIV **virus** load, we conclude that QRT-PCR calculating the level of BCR-ABL target is mainly useful to evaluate the MRD during the follow up and the response of imatinib treatment. However the BCR/ABL load does not allow to evaluate the number of oncogenic targets at the beginning of the treatment.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Pathology - Therapy 12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Gerontology 24500
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Molecular Genetics (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Parts, Structures, & Systems of Organisms
Philadelphia chromosome

IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, immune system disease, neoplastic disease, therapy
Leukemia, Myeloid, Chronic (MeSH)

IT Diseases
minimum residual disease: neoplastic disease

IT Chemicals & Biochemicals
Bcr-Abl mRNA [Bcr-Abl messenger RNA]: expression, regulation; imatinib mesylate [STI-571]: antineoplastic-drug, efficacy
IT Miscellaneous Descriptors
cytogenetic response; genetic load
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): adult, aged, aged/80 and over, middle age, patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 220127-57-1 (imatinib mesylate)
152459-95-5 (imatinib mesylate)
220127-57-1 (STI-571)
152459-95-5 (STI-571)
GEN human BCR-ABL gene (Hominidae): fusion gene, oncogene, regulation

L66 ANSWER 41 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:216183 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100216183
TITLE: Activity of a specific **inhibitor** of the BCR-**ABL** tyrosine **kinase** in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome.
AUTHOR(S): Druker, Brian J. [Reprint author]; Sawyers, Charles L.; Kantarjian, Hagop; Resta, Debra J.; Reese, Sofia Fernandes; Ford, John M.; Capdeville, Renaud; Talpaz, Moshe
CORPORATE SOURCE: Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd., L592, Portland, OR, 97201, USA
drukerb@ohsu.edu
SOURCE: New England Journal of Medicine, (April 5, 2001) Vol. 344, No. 14, pp. 1038-1042. print.
CODEN: NEJMAG. ISSN: 0028-4793.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 2001
Last Updated on STN: 18 Feb 2002

AB Background: BCR-ABL, a constitutively activated tyrosine kinase, is the product of the Philadelphia (Ph) chromosome. This enzyme is present in **virtually** all cases of chronic myeloid leukemia (CML) throughout the course of the disease, and in 20 percent of cases of acute lymphoblastic leukemia (ALL). On the basis of the substantial activity of the inhibitor in patients in the chronic phase, we evaluated STI571 (formerly known as CGP 57148B), a specific **inhibitor** of the BCR- **ABL** tyrosine **kinase**, in patients who had CML in blast crisis and in patients with Ph-chromosome-positive ALL. Methods: In this dose-escalating pilot study, 58 patients were treated with STI571; 38 patients had myeloid blast crisis and 20 had ALL or lymphoid blast crisis. Treatment was given orally at daily doses ranging from 300 to 1000 mg. Results: Responses occurred in 21 of 38 patients (55 percent) with a myeloid-blast-crisis phenotype; 4 of these 21 patients had a complete hematologic response. Of 20 patients with lymphoid blast crisis or ALL, 14 (70 percent) had a response, including 4 who had complete responses. Seven patients with myeloid blast crisis continue to receive treatment and remain in remission from 101 to 349 days after starting the treatment. All but one patient with lymphoid blast crisis or ALL has relapsed. The most frequent adverse effects were nausea, vomiting, edema, thrombocytopenia, and neutropenia. Conclusions: The BCR-**ABL**

tyrosine kinase inhibitor STI571 is well tolerated and has substantial activity in the blast crises of CML and in Ph-chromosome-positive ALL.

CC Neoplasms - Blood and reticuloendothelial neoplasms 24010
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Molecular Genetics (Biochemistry and Molecular Biophysics); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Diseases
acute lymphoblastic leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Lymphocytic, Acute (MeSH)

IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
BCR-ABL: tyrosine kinase; Philadelphia chromosome; STI571 [CGP 571148B]: antineoplastic-drug, enzyme inhibitor-drug

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 152459-95-5 (STI571)
152459-95-5 (CGP 571148B)

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ACCESSION NUMBER: 2001:240134 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100240134
TITLE: Effect of a selective **Abl** tyrosine **kinase inhibitor**, STI571, on in vitro growth of BCR-ABL-positive acute lymphoblastic leukemia cells.
AUTHOR(S): Kawaguchi, Y. [Reprint author]; Jinnai, I.; Nagai, K.; Yagasaki, F.; Yakata, Y.; Matsuo, T.; Kuriyama, K.; Tomonaga, M.
CORPORATE SOURCE: Department of Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University School of Medicine, 1-12-4 Sakamoto, Nagasaki, 852-8523, Japan
SOURCE: Leukemia (Basingstoke), (**April**, 2001) Vol. 15, No. 4, pp. 590-594. print.
CODEN: LEUKED. ISSN: 0887-6924.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 May 2001

Last Updated on STN: 18 Feb 2002

AB By employing a new semi-quantitative assay system that includes co-culturing leukemia cells with the mouse bone marrow-derived stromal cell line MS-5, we examined the suppressive effect of a selective **inhibitor** of **ABL** tyrosine **kinase**, STI571, on acute lymphoblastic leukemia (ALL) cells with BCR-ABL fusion. Leukemic blast cells from eight patients with B-precursor ALL, including three patients with BCR-ABL-positive ALL, were cultured on monolayers of MS-5 cells for 3 weeks with or without addition of variable amounts of STI571. In all cases, cobblestone areas (CAs) were formed, showing clear linear cell dose-dependent curves, allowing quantitative assessment of blast cell growth. The progenitor frequencies obtained by this direct CA-forming cell (CAFC) assay were equivalent to ALL progenitor frequencies assessed by the standard limiting dilution assay. The number of CAFCs ranged from 12.3 to 140.3/104 cells. In BCR-ABL-positive ALL patients, CA-containing cells were examined by FISH, and all contained BCR-ABL fusion genes. STI571 inhibited CA formation of BCR-ABL-positive ALL cells **virtually** 100% at 0.1-1.0 mumol/l. None of the five BCR-ABL-negative ALL patients showed this growth inhibition by STI571 at 0.1-1.0 mumol/l. Our results indicate that STI571 selectively inhibits in vitro growth of BCR-ABL-positive ALL cells.

CC Neoplasms - Therapeutic agents and therapy 24008
Pathology - Therapy ·12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Pharmacology; Tumor Biology

IT Diseases
BCR-ABL fusion gene-positive acute lymphoblastic leukemia: blood and lymphatic disease, neoplastic disease, drug treatment, in-vitro cell study

IT Chemicals & Biochemicals
ST 1571: antineoplastic-drug, **Abl** tyrosine **kinase** **inhibitor**, in-vitro tumor cell growth inhibitory effects

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L66 ANSWER 43 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:209936 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200209936
TITLE: Activity of the **ABL**-tyrosine **kinase** **inhibitor** Glivec (STI571) in Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) relapsing after allogeneic stem cell transplantation (allo-SCT).
AUTHOR(S): Ottmann, Oliver G. [Reprint author]; Wassmann, Barbara [Reprint author]; Pfeifer, Heike [Reprint author]; Scheuring, Urban [Reprint author]; Thiede, Christian; Brueck, Patrick [Reprint author]; Binckebank, Anja [Reprint author]; Atta, Johannes [Reprint author]; Martin, Hans [Reprint author]; Gschaidmeier, Harald; Hoelzer, Dieter [Reprint author]

CORPORATE SOURCE: Dept. of Hematology, J.W. Goethe University, Frankfurt, Germany
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 589a-590a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Mar 2002
Last Updated on STN: 27 Mar 2002

AB The prognosis of patients with Ph+/bcr-abl+ ALL who relapse after alloSCT is poor. Glivec (imatinib mesylate) is an **inhibitor** of the **ABL** tyrosine **kinase** with potent antileukemic activity in advanced Ph+ALL, although the duration of response is usually short. The clinical effects of Glivec on Ph+ALL recurring after alloSCT have not been established. We analysed 20 consecutive Ph+ALL patients who relapsed subsequent to alloSCT and were enrolled in multicenter clinical trials of Glivec (supported by Novartis). 2 pts. had received Glivec previously to enable transplantation. Glivec as a single agent induced a CR with PB recovery in 11 pts. (55%) and a complete leukemic response with persistent cytopenias in 4 pts. (20%). 5 pts. were refractory, including 1 early death on day 11 due to generalized leukemic organ infiltration. In CR patients, Ph+ cells became undetectable by cytogenetic and FISH analysis. Donor chimerism levels in responding patients increased from a pre-study median of 83% in PB and 64% in BM to 98% in both PB and BM within four weeks of starting Glivec. Concomitant treatment with immunosuppressive agents, **antiviral** and antifungal agents was feasible without apparent severe drug interactions. 10 of 15 responding patients relapsed after a median treatment duration of 5 months (range 8-33 mos.) one pat. died in CR at 3 mos. of transplant-related causes. A complete remission is ongoing in 4 pts. after 6, 10, 46 and 78 weeks on Glivec, respectively. One patient remains in complete molecular remission, based on quantitative RT-PCR (Taqman), after 1.5 years of treatment. In conclusion, Glivec is highly effective as initial treatment of relapsed Ph+ALL subsequent to alloSCT, with a favorable safety profile. A prolonged CR is achieved in a small subset of patients and molecular remissions are rare. Additional therapeutic modalities are required to prevent relapses in the majority of patients with advanced Ph+ALL; these will be explored in ongoing and future prospective clinical trials.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Immunological processes and allergy 22018
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - Immunopathology, tissue immunology 34508
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506
Chemotherapy - Antifungal agents 38508
IT Major Concepts

Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Parts, Structures, & Systems of Organisms
Philadelphia chromosome; stem cell: blood and lymphatics, graft

IT Diseases
Philadelphia chromosome positive acute lymphoblastic leukemia: blood and lymphatic disease, immune system disease, neoplastic disease, therapy

IT Chemicals & Biochemicals
ABL-tyrosine kinase: fusion protein; STI571: enzyme inhibitor-drug, pharmacodynamics; antifungal drug: antifungal-drug, antiinfective-drug; antiviral drug: antiinfective-drug, antiviral-drug; immunosuppressive drug: immunologic-drug, immunosuppressant-drug

IT Methods & Equipment
allogenic stem cell transplantation: therapeutic method

IT Miscellaneous Descriptors
disease relapse; donor chimerism; drug efficacy; molecular remission; Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 98037-52-6 (ABL-tyrosine kinase)
152459-95-5 (STI571)

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ACCESSION NUMBER: 2002:241220 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200241220
TITLE: Implications of Bim in abnormal hematopoiesis of chronic myelogenous leukemia (CML).
AUTHOR(S): Kuribara, Ryoko [Reprint author]; Honda, Hiroaki; Shinjyo, Tetsuharu; Hirai, Hisamaru; Ozawa, Keiya [Reprint author]; Inaba, Toshiya
CORPORATE SOURCE: Dept. of Hematology, Jichi Medical School, Tochigi, Japan
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 467a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Apr 2002
Last Updated on STN: 17 Apr 2002

AB We and others have identified two pivotal signaling pathways that regulate cytokine-initiated cell survival of hematopoietic progenitors. One pathway is involved in the upregulation of Bcl-xL through activation of STAT, while the other is implicated in the downregulation of Bim, a BH3-only cell death activator of the Bcl-2 superfamily, under the control of Ras/PI3-kinase. Because the latter pathway was turned out to be essential for cell survival, and because leukemic cells frequently acquire cytokine-independent cell growth, we tested whether Bim is one of the major molecular targets of leukemogenic chimeras formed by nonrandom chromosomal translocations. We

found that the enforced expression of Bcr-Abl tyrosine kinase in cytokine dependent cells reverses apoptosis due to cytokine starvation through upregulation of Bcl-xL and downregulation of Bim. Protein expression levels of Bim were found to be uniformly low in five cell lines established from leukemic cells after blastic crisis of CML and in six cell lines established from Ph1 chromosome-positive ALL. Moreover, STI571, a specific **inhibitor** of **Abl kinase**, induced Bim in these leukemia cells. In contrast, the expression levels of Bcl-xL were diverged between these cell lines and were not affected by STI571. To test whether Bcr-Abl is implicated in abnormal hematopoiesis in the chronic phase of CML through downregulating Bim, we tested its expression in hematopietic progenitors of p210BCR-ABL transgenic mice, **virtually** all of which spontaneously develop CML within 6 months after birth. We amplified hematopoietic progenitors by serum-free short-term culture of bone marrow cells from the transgenic mice and their normal littermates using thrombopoietin and stem cell factor, and separated early progenitors (Scal+ckit+Lin-) using magnet beads-based technique. These cells proliferated and differentiated for more than 1 week in the presence of these cytokines, while they underwent rapid apoptosis in cytokine-free medium. Progenitors from the transgenic mice survived longer than those from normal littermates in cytokine-free medium and this survival advantage was reversed by STI571. Real-time quantitive RT-PCR and immunoblot analysis revealed induction of Bim by cytokine withdrawal in progenitors from normal littermates, while expression levels of Bcl-xL were not altered. In contrast, Bim was not induced by cytokine withdrawal in those from the transgenic mice. STI571 induced Bim in progenitors from BCR-ABL transgenic mice cultured in the absence of cytokines, suggesting that the downregulation of Bim by Bcr-Abl contributes to survival advantage of progenitors expressing Bcr-Abl in cytokine-free condition. Again expression levels of Bcl-xL were not altered by cytokine deprivation in the presence or absence of the Abl inhibitor. CML-like accumulation of white blood cells in bone marrow and peripheral blood was reported to be found in Bim-deficient mice. Taken together, these results indicated that BCR-ABL contributes to leukemogenesis in the chronic phase of CML through protecting early progenitors from apoptosis by downregulating Bim expression.

CC General biology - Symposia, transactions and proceedings 00520
Clinical biochemistry - General methods and applications 10006
Pathology - General 12502
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Clinical Chemistry (Allied Medical Sciences); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Parts, Structures, & Systems of Organisms
Ph-1 chromosome, Philadelphia-1 chromosome; myelogenous cell: blood and lymphatics, immune system

IT Diseases
Ph-1 chromosome-positive ALL: blood and lymphatic disease, immune system disease, neoplastic disease, Ph-1 chromosome-positive acute lymphoblastic leukemia

IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, immune

system disease; neoplastic disease, complications, pathology
Leukemia, Myeloid, Chronic (MeSH)
IT Diseases
hematopoiesis abnormality: blood and lymphatic disease
IT Chemicals & Biochemicals
Bcl-x-L: expression; Bcr-Abl: expression; Bim: expression, regulation;
STI571: antineoplastic-drug, enzyme inhibitor-drug
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 152459-95-5 (STI571)

L66 ANSWER 45 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:186446 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200186446
TITLE: Effects of aminopeptidase inhibitors on STI571 resistant CML cell lines.
AUTHOR(S): Sawafuji, Kanoko [Reprint author]; Miyakawa, Yoshitaka [Reprint author]; Weisberg, Ellen; Griffin, James D.; Ikeda, Yasuo [Reprint author]; Kizaki, Masahiro [Reprint author]
CORPORATE SOURCE: Internal Medicine, Keio University School of Medicine, Tokyo, Japan
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 309a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

AB A tyrosine kinase inhibitor, STI571 (Gleevec, Novartis Pharmaceuticals), has been shown to be effective for the treatment of chronic myelogenous leukemia (CML). It inhibits tyrosine kinase activity of ABL and induces apoptosis of CML cells. However drug resistance develops commonly in blast phase, and has become a significant therapeutic problem. We examined the effects of aminopeptidase inhibitors on a CML cell line (K562) and an STI571-resistant subline of K562. The aminopeptidase inhibitor ubenimex (bestatin) from Streptomyces olivoreticuli has been previously demonstrated to prolong disease free survival in adult myelogenous leukemia in combination with chemothempy. Recently ubenimex was also shown to directly induce apoptosis of leukemic cell lines in vitro. Ubenimex and another aminopeptidase inhibitor, actinonin, inhibited the proliferation of both K562 cells and STI571-resitant K562 cells to an equal degree and also induced their apoptosis in a dose dependent and time dependent manner. The proliferation of STI571-resistant cells was inhibited by actinonin at 10 mug/ml by 46% and 100 mug/ml by 62%, respectively. Ubenimex at 100 mug/ml inhibited resistant cells by 41%.

Ubenimex and actinonin induced the activation of caspase 3, however the induction of apoptosis was not rescued by caspase inhibitors (Z-VAD), demonstrating the existence of caspase-independent pathways. In contrast to STI571, ubenimex did not inhibit tyrosine phosphorylation of BCR/ABL proteins in K562 cells. When ubenimex and actinonin were used in combination with STI571 in STI571-resistant cells and parent K562 cells, no synergy was observed. STI571 induced erythroid differentiation of parent K562 cells. In contrast, ubenimex did not induce erythroid differentiation but upregulated CD13 expression (aminopeptidase N). The aminopeptidase inhibitors induced cell cycle arrest in parent K562 cells and STI571-resistant cells. In these STI571-resistant cells, the multidrug resistant gene (MDR) product was not increased, but Bcr-Abl expression was augmented without gene amplification. In preliminary experiments, serine phosphorylation of Akt and GSK-3 was inhibited by ubenimex in K562 cells, and the anti-apoptotic factor, Bax, was also induced. Further studies will be needed to determine if these viability signaling pathways are involved in the molecular mechanism of aminopeptidase inhibitor-induced apoptosis in STI571-resistant cells. Overall, these results suggest that STI571-resistant cells are not cross-resistant to aminopeptidase inhibitors, and support the potential clinical use of these drugs in combination therapy for STI571-resistant CML patients.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Physiology and biochemistry of bacteria 31000
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology; Tumor Biology

IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, immune system disease, neoplastic disease, drug therapy
Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
Akt: phosphorylation; Bax; Bcr/abl: expression; CD13: expression, regulation; GSK-3: phosphorylation; STI571: enzyme inhibitor-drug; Z-VAD: enzyme inhibitor-drug; actinonin: enzyme inhibitor-drug; caspase 3: activation; ubenimex [bestatin]: antineoplastic-drug, enzyme inhibitor-drug

IT Miscellaneous Descriptors
drug dosage; Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
K562 cell line: apoptosis
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Streptomycetes and Related Genera 08840
Super Taxa
Actinomycetes and Related Organisms; Eubacteria; Bacteria;

Macroorganisms
Organism Name
Streptomyces olivoreticuli
Taxa Notes
Bacteria, Eubacteria, Microorganisms
RN 152459-95-5 (STI571)
13434-13-4 (actinonin)
169592-56-7 (caspase 3)
58970-76-6 (ubenimex)
58970-76-6 (bestatin)
GEN human MDR gene [human multidrug resistant gene] (Hominidae)

L66 ANSWER 46 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:153068 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200153068
TITLE: Anti-ABL tyrosine kinase intrabody promotes apoptosis in K562 cells.
AUTHOR(S): Xu, Dong [Reprint author]; Song, Junmin [Reprint author]; Li, Dong [Reprint author]; Verfaillie, Catherine M.; Zhao, Robert C. H. [Reprint author]
CORPORATE SOURCE: National Lab of Experimental Hematology, Institute of Hematology, PUMC and CAMS, Tianjin, China
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 146a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB The malignant transformation by p210BCR/ABL is critically dependent on its deregulated tyrosine kinase (TK) activity in the pathogenesis of chronic myelogenous leukemia (CML). In this study, we constructed a retroviral vector to express intracellular single-chain antibody (intrabody/ib) directed against ABL tyrosine kinase domain and investigated the effects of the intrabody on CML cell line K562. The recombinant retrovirus MSCV-ib-eGFP combines eGFP gene and genes encoding the immunoglobulin heavy chain and light chain variable regions of 8E9, an anti-ABL monoclonal antibody. K562 cells were transduced with MSCV-ib-eGFP or MSCV-eGFP retrovirus. K562-ib as an in vitro cell model and K562-eGFP as control were obtained by sorting eGFP+ cells with FACS. Cytoplasm expression of the intrabody **inhibited** tyrosine **kinase** activity of c-**ABL** and p210BCR/ABL protein by 76% followed by a 48% down-regulation of the whole cell TK activity in k562 cells. This subsequently led to increased susceptivity of K562-ib cells to apoptosis inducing stimulus in comparison with K562-eGFP cells or K562 cells: they developed markedly earlier apoptotic changes when treated with etoposide; more K562-ib cells underwent growth cessation and exhibited apoptotic morphology after the removal of serum from the culture media. Expression of the eGFP and the intrabody has been stable for at least half a year in vitro and for more than 80 days in vivo. Finally, the intrabody significantly decreased tumorigenicity of K562 cells in vivo. The effects of the intrabody on K562 cells have led to its possible use for both fundamental research and clinical application for CML.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Enzymes - General and comparative studies: coenzymes 10802

Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease, etiology
Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
8E9 immunoglobulin heavy chain; 8E9 immunoglobulin light chain; ABL tyrosine kinase: expression; anti-ABL tyrosine kinase intrabody: expression; tyrosine kinase: regulation

IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
K562 cell line: apoptosis, regulation
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
retrovirus: gene vector
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 98037-52-6 (ABL tyrosine kinase)
80449-02-1 (tyrosine kinase)

GEN eGFP gene [enhanced green fluorescent protein gene]

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ACCESSION NUMBER: 2002:153059 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200153059
TITLE: Increase of proteosome mediated degradation of p27kip is associated to abnormal cell cycle regulation in CML cells.
AUTHOR(S): Andreu, Enrique J. [Reprint author]; Lledo, Elisa; Perez-Roger, Ignacio; Arbona, Cristina; Rifon, Jose J. [Reprint author]; Rocha, Eduardo [Reprint author]; Prosper, Felipe [Reprint author]
CORPORATE SOURCE: Cell Therapy Area, University Clinic of Navarra, Pamplona, Spain
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 144a. print.
Meeting Info.: 43rd Annual Meeting of the American Society

of Hematology, Part 1 Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB Expression of bcr-abl alters the regulation of cell cycle in CML cells. Recent studies have indicated that the cell cycle inhibitor p27kip is downregulated in bcr-abl positive cells. The goal of our study was twofold: to determine the role of p27kip downregulation on abnormal cell cycle regulation in bcr-abl cells and to assess the mechanism of p27kip regulation in bcr-abl cells. MO7E-p210 and Baf3-p210 cell lines and CD34 positive cells from CML patients and normal donors were incubated with STI 571 (bcr-abl kinase inhibitor). STI 571 induced a decreased in the percentage of bcr-abl cells in S-phase and had no effect on human normal CD34+ cells and this cell cycle arrest was associated with upregulation of p27kip in p210 expressing cells, assessed by immunoprecipitation and western blot analysis. The role of p27kip expression in bcr-abl positive cells was determined by transfection of a nonhydrolyzable p27kip retroviral vector that induced cell cycle arrest in G1 phase in bcr-abl positive cells. STI 571 did not induced any changes in the level of p27kip mRNA expression by northerm blot. Further, MO7E-p210 cells transfected with the luciferase reporter vector containing the promoter region of p27kip showed no increase in luciferase activity when incubated in the presence of STI 571. This indicates lack of transcriptional regulation of p27kip after inhibition of bcr-abl. Postranslational regulation was assessed with metabolic labeling with 35S-Met and pulse and chase analysis in Baf3-p210 cells. We observed a time dependent accumulation of p27kip after incubation with STI 571 or lactacystin (inhibitor of proteosome) in comparison with control cells bcr-abl positive cells not treated with STI 571. Half life of p27kip increased in the presence of STI 571. In conclusion, cell cycle progression in bcr-abl cells is associated with a downregulation of p27kip. Inhibition of bcr-abl results in an increase in p27kip levels and a decreased proliferation. Levels of p27kip are regulated by increasing the proteasome-mediated degradation of p27kip while transcriptional regulation does not play a significant role in controlling p27kip expression. In conclusion, bcr-abl promotes progression of the cell cycle in CML cells at least in part by increasing the degradation of p27kip.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Pathology - General 12502
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Tumor Biology
IT Parts, Structures, & Systems of Organisms
CD34 positive cell: blood and lymphatics, immune system

IT Diseases
CML: blood and lymphatic disease, immune system disease, neoplastic disease, pathology, chronic myeloid leukemia
Leukemia, Myeloid, Chronic (MeSH)
IT Chemicals & Biochemicals
STI 571: antineoplastic-drug, enzyme inhibitor-drug; bcr-abl; lactacystin; p210: expression; p27kip: expression, regulation
IT Miscellaneous Descriptors
cell cycle; cell cycle regulation; Meeting Abstract; Meeting Poster
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
MO7E cell line
Taxa Notes
Animals
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Baf3 cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing **Viruses**; **Viruses**; Microorganisms
Organism Name
retrovirus: gene vector
Taxa Notes
DNA and RNA Reverse Transcribing **Viruses**, Microorganisms, **Viruses**
RN 152459-95-5 (STI 571)
133343-34-7 (lactacystin)

L66 ANSWER 48 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:153054 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200153054
TITLE: Identification of multiple genes implicated in the pathogenesis of CML by subtractive hybridization.
AUTHOR(S): Salesse, Stephanie [Reprint author]; Verfaillie, Catherine M. [Reprint author]
CORPORATE SOURCE: Stem Cell Institute, University of Minnesota, Minneapolis, MN, USA
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 142a-143a. print.
Meeting Info.: 43rd Annual Meeting of the American Society

of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB The p210BCR-ABL chimeric protein plays a central role in the pathogenesis of Chronic Myelogenous Leukemia (CML). Intensive research has elucidated many of the signal pathways activated by p210BCR-ABL. Activation of such pathways may affect the expression of genes that confer the malignant phenotype. However, few studies that address p210BCR-ABL-dependent gene expression are available and only a few downsteam targets have been identified. In order to further define such downstream genes, we performed a subtractive hybridization between cord blood (CB) CD34+ cells transduced with an MSCV-retrovirus vector containing either eGFP alone or p210BCR-ABL-IRES-eGFP. 150 subtracted clones expressed in p210-eGFP but not eGFP-transduced CD34+ cells have been sequenced and analyzed. 54% represent novel proteins and 46% are homologous to known genes. Northern blot and Real time PCR analysis were used to confirm overexpression of these sequences in CD34+ progenitors from 5-10 p210BCR-ABL-transduced CB samples as wells as 5-10 CD34+ cell populations from early chronic phase CML patients versus GFP-transduced CB or normal bone marrow CD34+. To date, we identified 25 differentially expressed mRNA's, 10 of which correspond to unknown sequences, and 15 to known genes. Overexpression of most known genes was confirmed at the protein level, by Western blot. Intriguingly, treatment of BCR-ABL-positive cells with the **Abl** -specific tyrosine **kinase inhibitor**, STI571, induced a decrease in expression at the mRNA as well as protein level of 11 genes but did not affect expression of 4 genes suggesting that the Abl-TK is responsible for upregulating some but not all overexpressed genes in CML CD34+ cells. A number of overexpressed genes are implicated in cellular processes that are disturbed in CML like MEK6 (MAPK pathways), E2 (ubiquitin pathways), the differentiation inhibitory factor Nm23 and the nucleoporin NUP98. However, other genes such as Ran (nucleocytoplasmic transport), and SRPK1 (mRNA splicing) suggest that novel pathways may be deregulated in CML. Thus, the identification of such downstream molecules will lead to important new insights in the molecular mechanisms underlying CML and may identify critical targets for novel therapies for this disease.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Genetics of bacteria and viruses 31500
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
IT Major Concepts

Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Parts, Structures, & Systems of Organisms
CD34 positive cell: blood and lymphatics, immune system; bone marrow: blood and lymphatics, immune system; cord blood: blood and lymphatics

IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, immune system disease, neoplastic disease, etiology, genetics, CML Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
Abl-TK; CD34; E2; MEK6; NUP98: nucleoporin; Nm23; STI571: antineoplastic-drug, enzyme inhibitor-drug; eGFP [enhanced green fluorescent protein]: expression; mRNA [messenger RNA]; p210-BCR-ABL-IRES-eGFP: expression, fusion protein

IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
retrovirus: gene vector
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 152459-95-5 (STI571)
180033-16-3 (ENHANCED GREEN FLUORESCENT PROTEIN)

GEN human p210-BCR-ABL gene (Hominidae)

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ACCESSION NUMBER: 2001:91705 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100091705
TITLE: Expression of a truncated first exon BCR sequence in chronic myelogenous leukemia cells blocks cell growth and induces cell death.
AUTHOR(S): Wang, Yan; Liu, Jiaxin; Wu, Yun; Luo, Weiping; Lin, Sue-Hwa; Lin, Hui; Hawk, Natalyn; Sun, Tong; Guo, Jie Qiang; Estrov, Zeev; Talpaz, Moshe; Champlin, Richard; Arlinghaus, Ralph B. [Reprint author]
CORPORATE SOURCE: Department of Molecular Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX, 77030, USA
rarlingh@mdanderson.org
SOURCE: Cancer Research, (January 1, 2001) Vol. 61, No. 1, pp. 138-144. print.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2001
Last Updated on STN: 12 Feb 2002

AB We have shown that a deletion mutant form of Bcr (Bcr(64-413)) is a strong inhibitor of the tyrosine kinase of Bcr-Abl in vitro and also inhibits its oncogenic growth effects (Liu et al., Cancer Res., 56: 5120-5124, 1996). To determine the effects of this Bcr-Abl kinase inhibitor on chronic myelogenous leukemia (CML) cells, we cloned BCR(64-413) into a recombinant, replication-defective adenovirus to express useful quantities of Bcr(64-413) in a wide variety of cells in culture. Infection of Cos1 cells with plaque-purified virus at a multiplicity of infection of 20-40 induced high expression of Bcr(64-413) as detected by Western blotting. Infection of hematopoietic cells at modest multiplicities of infection (20-40) required special conditions involving shifting cycling cells to a nongrowing condition involving serum starvation and cell crowding. Under these conditions, both Bcr-Abl-positive and -negative hematopoietic cells can be efficiently infected by adenovirus, as demonstrated by 5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside staining of cells infected by beta-galactosidase (beta-GAL) adenovirus. We found that expression of Bcr(64-413) in Bcr-Abl-positive K562 and BV-173 cells, but not Bcr-Abl-negative SMS-SB cells, increased cell-cell clumping and inhibited cell growth. In contrast to the effects of the Bcr(64-413) adenovirus, the beta-GAL adenovirus, despite infecting both types of cells, did not block growth or increase cell-cell clumping of Bcr-Abl-positive and -negative hematopoietic cells. Expression of Bcr(64-413) protein in primary cultures of cells from CML patients with active disease interfered with cell growth, induced apoptosis (as measured by annexin staining), and increased cell-cell clumping, whereas the beta-GAL adenovirus and mock-infected cells lacked these effects. In contrast, normal marrow cells did not exhibit these effects on infection with Bcr(64-413) adenovirus. We conclude from these findings that Bcr(64-413) interferes with the oncogenic effects of Bcr-Abl and therefore has the potential for use in therapy of CML.

CC Blood - Blood and lymph studies 15002
Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Virology - Animal host viruses 33506

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Tumor Biology

IT Parts, Structures, & Systems of Organisms
hematopoietic cells: blood and lymphatics

IT Diseases
chronic myelogenous leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Myeloid, Chronic (MeSH)

IT Chemicals & Biochemicals
5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside: stain; BCR: expression, truncated first exon sequence; Bcr(64-413): expression

IT Methods & Equipment
Western blotting: analytical method, detection/labeling techniques

IT Miscellaneous Descriptors
apoptosis; cell death; cell growth; cell-cell clumping

ORGN Classifier
Adenoviridae 03116
Super Taxa
dsDNA Viruses; Viruses; Microorganisms
Organism Name
beta-galactosidase adenovirus

Taxa Notes
Double-Stranded DNA **Viruses**, Microorganisms, **Viruses**
ORGN Classifier
Cercopithecidae 86205
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Cos1 cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Mammals, Nonhuman Vertebrates, Nonhuman Primates, Primates, Vertebrates
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
BV-173 cell line
K562 cell line
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
virus: plaque-purified
Taxa Notes
Microorganisms, **Viruses**
RN 7240-90-6 (5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside)

L66 ANSWER 50 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:312514 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100312514
TITLE: Functional link of BCR/ABL oncogenic tyrosine kinase and RAD51 double strand break repair protein in DNA damage response.
AUTHOR(S): Slupianek, A. [Reprint author]; Tombline, G.; Schmutte, C.; Nieborowska-Skorska, M.; Malecki, M.; Fishel, R.; Skorski, T.
CORPORATE SOURCE: Center for Biotechnology, Temple University, Philadelphia, PA, USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 509a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002
AB Double-strand breaks (DSBs), probably the most disruptive type of lesion in DNA, may arise after exposure to DNA-damaging agents. If left unrepaired, DSBs lead to broken chromosomes and cell death. Philadelphia chromosome-positive (Ph1) leukemias expressing BCR/ABL oncogenic tyrosine kinases are usually resistant to DNA damaging agents (cytostatics, radiation) inducing DSBs. Using representational differences analysis (RDA) followed by Northern

blotting and Western blotting we found that BCR/ABL kinase induces overexpression of RAD51 in hematopoietic cell lines and in chronic myelogenous leukemia (CML) cells. RAD51 is a member of conserved family of eukaryotic proteins related to **Escherichia** coli RecA protein, which plays a central role in prokaryotic response to DNA damage. Both, RecA and RAD51 promote homology-dependent repair of DSBs. BCR/ABL-induced elevation of RAD51 expression is due to the STAT5-mediated transactivation of RAD51 promoter and the prevention of RAD51 cleavage by inhibition of caspase-3. BCR/ABL is in complex with RAD51 and induces its phosphorylation on Y315, which increases RAD51 cytoplasmic-nuclear shuttling and assembly on DNA lesions (DSBs). Using the in vivo DSBs repair model in which DSBs are induced in the green fluorescent protein (GFP) sequence and their reparation is assessed by the appearance of GFP+ cells, we found that RAD51 is responsible for enhanced DSBs repair in BCR/ABL-transformed cells. Inhibition of RAD51 expression and/or function by the antisense cDNA or the Y315F mutant reduced almost completely drug resistance in BCR/ABL-transformed cells. Incubation of BCR/ABL-positive cells with the **ABL kinase inhibitor** STI571 caused downregulation of expression of RAD51 and abrogated drug resistance. Expression of exogenous RAD51 elevated the total amount of RAD51 protein and partially rescued drug resistance in these cells. In contrast to drug-induced apoptosis, modulation of RAD51 expression did not affect the susceptibility of normal and BCR/ABL-transformed cells to apoptosis induced by growth factor withdrawal. Moreover, RAD51 does not seem to be directly involved in regulation of G2/M cell cycle phase, P-glycoprotein or caspase-3, which may be involved in drug resistance. Instead, BCR/ABL-dependent overexpression of RAD51 is responsible for enhanced reparation of drug-induced lethal DNA lesions (DSBs), which decrease activation/accumulation of the "DNA damage sensor" p73 and reduce the pro-apoptotic signaling from the nucleus. Thus, BCR/ABL-induced and RAD51-mediated DNA repair represents a novel mechanism contributing to drug resistance in Ph1 leukemias.

CC Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
General biology - Symposia, transactions and proceedings 00520
Genetics - General 03502
Genetics - Human 03508
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Tumor Biology

IT Diseases
leukemia: blood and lymphatic disease, neoplastic disease, drug resistance, tumor development
Leukemia (MeSH)

IT Chemicals & Biochemicals
BCR-ABL oncogenic tyrosine kinase: DNA damage response role, RAD-51 double strand break repair protein functional link, drug resistance role, tumor development role

IT Miscellaneous Descriptors
Meeting Abstract

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

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ACCESSION NUMBER: 2000312477 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100312477
TITLE: Implications of Bim, a BH3-only member of Bcl-2 superfamily, in abnormal hematopoiesis of chronic myelogenous leukemia.
AUTHOR(S): Kuribara, R. [Reprint author]; Honda, H.; Shinjyo, T. [Reprint author]; Inukai, T.; Sugita, K.; Nakazawa, S.; Hirai, H.; Ozawa, K. [Reprint author]; Inaba, T. [Reprint author]
CORPORATE SOURCE: Depts. of Hemat. and Mol. Biology, Jichi Med. School, Tochigi, Japan
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 347a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB Dysregulation of apoptosis by BCR-ABL in hematopoietic progenitors has been implicated in the leukemogenesis of CML. However, it is not directly demonstrated because no appropriate experimental system is available for the chronic phase of CML. We previously established p210BCR-ABL transgenic mice, virtually all of which spontaneously develop a CML-like myeloproliferative disease within eight months after birth. We amplified hematopoietic progenitors in vitro by serum-free short-term culture of bone marrow cells from the transgenic mice and their normal littermates using TPO and SCF. Early (Sca-1+c-kit+Lin-) and late (Sca-1-c-kit+Lin-) progenitors were separated using magnetic beads and the cells were then cultured in cytokine-free medium. Early progenitors from the transgenic mice survived longer than those from normal littermates, which rapidly underwent apoptosis. Moreover, this survival advantage was reversed by STI571, a specific inhibitor of the BCR-ABL tyrosine kinase. In contrast, late progenitors from the transgenic mice underwent apoptosis in the same time course as those from normal littermates and STI571 did not affect their survival. These results suggested that the kinase contributes to leukemogenesis through protecting early progenitors from apoptosis due to cytokine starvation in the chronic phase of CML. We next tried to elucidate its molecular mechanism. Using murine IL-3-dependent cells, we have demonstrated that the simultaneous downregulation of Bcl-xL and upregulation of Bim, a BH3-only member of cell death activators, is essential in cell death due to cytokine withdrawal and that enforced expression of BCR-ABL in these cells reverses apoptosis through the upregulation of Bcl-xL and the downregulation of Bim. To identify a key downstream factor of BCR-ABL in CML, we tested the expression of the Bcl-2 superfamily members in cell lines established from CML patients after blastic crisis. The expression levels of Bim were uniformly low in these cells. Moreover, Bim expression was upregulated in cells undergoing apoptosis induced by STI571. In contrast, the expression levels of Bcl-2 or Bcl-xL were diverged between cell lines and STI571 did not downregulate them. Taken together, these results suggested that BCR-ABL contributes to leukemogenesis in the chronic phase of CML by downregulating Bim expression in early hematopoietic progenitors.

CC Biochemistry studies - Proteins, peptides and amino acids 10064
General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Blood - Blood and lymph studies 15002

Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Tumor Biology
IT Diseases
blast crisis: neoplastic disease
Blast Crisis (MeSH)
IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Myeloid, Chronic (MeSH)
IT Chemicals & Biochemicals
Bcl-2: expression; Bim: Bcl-2 superfamily BH3-only member, expression, regulation; STI571: BCR-**ABL** tyrosine **kinase inhibitor**
IT Miscellaneous Descriptors
apoptosis; hematopoiesis; signal transduction; Meeting Abstract; Meeting Poster
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model, transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 152459-95-5 (STI571)

L66 ANSWER 52 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:516953 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799816156
TITLE: The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells.
AUTHOR(S): Deininger, Michael W. N.; Goldman, John M.; Lydon, Nicholas; Melo, Junia V. [Reprint author]
CORPORATE SOURCE: Dep. Haemacol.-RPMS, Hammersmith Hosp., Ducane Road, London W12 0NN, UK
SOURCE: Blood, (1997) Vol. 90, No. 9, pp. 3691-3698.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1997
Last Updated on STN: 10 Dec 1997
AB The Philadelphia chromosome found in **virtually** all cases of chronic myeloid leukemia (CML) and in about one third of the cases of adult acute lymphoblastic leukemia is formed by a reciprocal translocation between chromosomes 9 and 22 that results in the fusion of BCR and ABL genetic

sequences. This BCR-ABL hybrid gene codes for a fusion protein with deregulated tyrosine kinase activity that can apparently cause malignant transformation. CGP571488, a 2-phenylaminopyrimidine derivative, has been shown to selectively inhibit the tyrosine kinase of ABL and BCR-ABL. We report here that this compound selectively suppresses the growth of colony-forming unit-granulocyte/macrophage (CFU-GM) and burst-forming unit-erythroid derived from CML over a 2-logarithmic dose range with a maximal differential effect at 1.0 mu-mol/L. However, almost all CML colonies that grow in the presence of 1.0 mu-mol/L CGP57148B are BCR-ABL-positive, which may reflect the fact that residual normal clonogenic myeloid precursors are infrequent in most patients with CML. We also studied the effects of CGP57148B on hematopoietic cell lines. Proliferation was suppressed in most of the BCR-ABL-positive lines; all five BCR-ABL-negative lines were unaffected. We conclude that this new agent may have significant therapeutic applications.

CC Genetics - Human 03508
Enzymes - Physiological studies 10808
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Blood and hematopoietic agents 22008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Development and Embryology - Morphogenesis 25508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Chemicals & Biochemicals
TYROSINE KINASE

IT Miscellaneous Descriptors
ACUTE LYMPHOBLASTIC LEUKEMIA; ANTINEOPLASTIC-DRUG; BLOOD AND LYMPHATIC DISEASE; BLOOD AND LYMPHATICS; BURST-FORMING UNIT-ERYTHROID; CD34-POSITIVE CELLS; CGP57148B; CHRONIC MYELOID LEUKEMIA; COLONY-FORMING UNIT-GRANULOCYTE/MACROPHAGE; GROWTH; HEMATOLOGY; IMMUNE SYSTEM; NEOPLASTIC DISEASE; ONCOLOGY; PATIENT; PHILADELPHIA CHROMOSOME; SURVIVAL; TYROSINE KINASE; 2-PHENYLAMINOPYRIMIDINE DERIVATIVE

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 80449-02-1 (TYROSINE KINASE)

L66 ANSWER 53 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:111156 BIOSIS Full-text
DOCUMENT NUMBER: PREV199698683291
TITLE: **Inhibition** of the **Abl** protein-tyrosine **kinase** in vitro and in vivo by a 2-phenylaminopyrimidine derivative.
AUTHOR(S): Buchdunger, Elisabeth [Reprint author]; Zimmermann, Jurg; Mett, Helmut; Meyer, Thomas; Mullet, Marcell; Druker, Brian J.; Lydon, Nicholas B.
CORPORATE SOURCE: Ciba Pharmaceuticals Div., Res. Dep., Ciba-Geigy Ltd., CH-4002 Basel, Switzerland
SOURCE: Cancer Research, (1996) Vol. 56, No. 1, pp. 100-104.
CODEN: CNREA8. ISSN: 0008-5472.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Mar 1996
Last Updated on STN: 13 Mar 1996

AB Oncogenic activation of Abl proteins due to structural modifications can occur as a result of **viral** transduction or chromosomal translocation. The tyrosine protein kinase activity of oncogenic Abl proteins is known to be essential for their transforming activity. Therefore, we have attempted to identify selective **inhibitors** of the **Abl** tyrosine protein **kinase**. Herein we describe an inhibitor (CGP 57148) of the Abl and platelet-derived growth factor (PDGF) receptor protein-tyrosine kinases from the 2-phenylaminopyrimidine class, which is highly active in vitro and in vivo. Submicromolar concentrations of the compound inhibited both v-Abl and PDGF receptor autophosphorylation and PDGF-induced c-fos mRNA expression selectively in intact cells. In contrast, ligand-induced growth factor receptor autophosphorylation in response to epidermal growth factor (EGF), insulin-like growth factor-1, and insulin showed no or weak inhibition by high concentrations of CGP 57148. c-fos mRNA expression induced by EGF, fibroblast growth factor, or phorbol ester was also insensitive to inhibition by CGP 57148. In antiproliferative assays, the compound was more than 30-100-fold more potent in inhibiting growth of v-abl-transformed PB-3c cells and v-sis-transformed BALB/c 3T3 cells relative to inhibition of EGF-dependent BALB/MK cells, interleukin-3-dependent FDC-PI cells, and the T24 bladder carcinoma line. Furthermore, anchorage-independent growth of v-abl- and v-sis-transformed BALB/c 3T3 cells was inhibited potently by CGP 57148. When tested in vivo, CGP 57148 showed antitumor activity at tolerated doses against tumorigenic v-abl- and v-sis-transformed BALB/c 3T3 cells. In contrast, CGP 57148 had no antitumor activity when tested using src-transformed BALB/c 3T3 cells. These findings suggest that CGP 57148 may have therapeutic potential for the treatment of diseases that involve abnormal cellular proliferation induced by Abl protein-tyrosine kinase deregulation or PDGF receptor activation.

CC Cytology - Animal 02506
Genetics - Animal 03506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Biophysics - Membrane phenomena 10508
Enzymes - Chemical and physical 10806
Urinary system - Pathology 15506
Endocrine - General 17002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Development and Embryology - Morphogenesis 25508
In vitro cellular and subcellular studies 32600

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Pharmacology; Tumor Biology; Urinary System (Chemical Coordination and Homeostasis)

IT Chemicals & Biochemicals
PROTEIN-TYROSINE KINASE

IT Miscellaneous Descriptors
BALB/C 3T3 CELL LINE; CELLULAR PROLIFERATION; ENZYME DEREGULATION; MOUSE CELL LINE; ONCOGENIC ACTIVATION; ONCOGENIC PROTEIN TRANSFORMING ACTIVITY; PLATELET DERIVED GROWTH FACTOR RECEPTOR ACTIVATION; THERAPEUTIC POTENTIAL; T24 BLADDER CARCINOMA

ORGN Classifier
Muridae 86375

Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 80449-02-1 (PROTEIN-TYROSINE KINASE)

L66 ANSWER 54 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:225301 BIOSIS Full-text
DOCUMENT NUMBER: PREV199497238301
TITLE: An active v-abl protein tyrosine kinase blocks immunoglobulin light-chain gene rearrangement.
AUTHOR(S): Chen, Yunn-Yi; Wang, Li Chun; Huang, Mary S.; Rosenberg, Naomi [Reprint author]
CORPORATE SOURCE: Immunol. Graduate Program, Dep. Pathol., Tufts Univ. Sch. Med., Boston, MA 02111, USA
SOURCE: Genes and Development, (1994) Vol. 8, No. 6, pp. 688-697.
CODEN: GEDEEP. ISSN: 0890-9369.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 May 1994
Last Updated on STN: 14 Jul 1994

AB Lymphoid cells transformed by Abelson murine leukemia virus have provided one of the classic models for study of early B-cell development and immunoglobulin rearrangement. Most of these cells have rearranged their heavy-chain locus but not their light chain genes, suggesting that an active v-abl protein interferes with this differentiation step. To test this hypothesis, light-chain gene structure was examined in pre-B cells transformed by temperature-sensitive mutants of the Abelson virus and in derivatives that survive at the nonpermissive temperature because they express a human BCL-2 gene. Our studies reveal that inactivation of the v-abl protein tyrosine kinase triggers high-frequency rearrangement of kappa and lambda light-chain genes. These events are accompanied by marked increases in the expression of RAG-1 and RAG-2 RNAs. These increases occur in the absence of protein synthesis but are dependent on inactivation of the v-abl protein tyrosine kinase. As documented in the accompanying paper (Klug et al., this issue), an active v-abl protein also suppresses the activity of NF-kappa-B/rel and expression controlled by the kappa intron enhancer. Together these data demonstrate that the v-abl protein specifically interferes with light-chain gene rearrangement by suppressing at least two pathways essential for this stage of B-cell differentiation and suggest that tyrosine phosphorylation is important in regulating RAG gene expression.

CC Genetics - Animal 03506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Enzymes - Chemical and physical 10806
Enzymes - Physiological studies 10808
Development and Embryology - Morphogenesis 25508
Genetics of bacteria and viruses 31500
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006
IT Major Concepts
Biochemistry and Molecular Biophysics; Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Immune System (Chemical Coordination and Homeostasis); Infection

IT Chemicals & Biochemicals
PROTEIN TYROSINE KINASE
IT Miscellaneous Descriptors
B CELL DIFFERENTIATION; DEVELOPMENT; GENE
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
Abelson murine leukemia virus
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 80449-02-1 (PROTEIN TYROSINE KINASE)

L66 ANSWER 55 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:228893 BIOSIS Full-text
DOCUMENT NUMBER: PREV199497241893
TITLE: Effects of herbimycin A and its derivatives on growth and differentiation of Ph-1-positive acute lymphoid leukemia cell lines.
AUTHOR(S): Sato, Seitetsu; Honma, Yoshio [Reprint author]; Hozumi, Motoo; Hayashi, Yasuhide; Matsuo, Yoshinobu; Shibata, Kiyoshi; Omura, Satoshi; Hino, Ken-Ichiro; Tomoyasu, Shigeru; Tsuruoka, Nobuyoshi
CORPORATE SOURCE: Dep. Chemotherapy, Saitama Cancer Center Research Inst., 818 Komuro, Ina, Saitama-362, Japan
SOURCE: Leukemia Research, (1994) Vol. 18, No. 3, pp. 221-228.
CODEN: LEREDD. ISSN: 0145-2126.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 May 1994
Last Updated on STN: 25 May 1994

AB The molecular basis of the Philadelphia chromosome (Ph-1) is a structurally altered c-abl (bcr/abl) gene which encodes an abnormally large protein with protein tyrosine kinase activity. Herbimycin A, an inhibitor of tyrosine kinase, preferentially inhibited the growth of Ph-1-positive acute lymphoid leukemia (ALL) cell lines, as well as Ph-1-positive chronic myeloid leukemia (CML) cell lines. Although noncytotoxic concentrations of herbimycin A induced erythroid differentiation of two CML-derived cell lines, K562 and KU812, in a previous study, the differentiation-inducing effect of herbimycin A on Ph-1-positive ALL cell lines was less strong. Herbimycin A enhanced some differentiation-associated properties of one Ph-1-positive ALL cell line, L2, but the effect of herbimycin A on the other Ph-1-positive ALL cell lines was cytotoxic rather than cytostatic (differentiation-inducing). Several derivatives of herbimycin A were synthesized and their effects on the cell proliferation of Ph-1-positive CML and ALL cell lines were examined. The sensitivities of the Ph-1-positive cell lines to herbimycin A derivatives were different from the data on the rat kidney cell line infected with Rous sarcoma virus (vsrc) derived from a previous study, suggesting bcr/abl kinase may differ in sensitivity from other tyrosine kinases. Moreover, the sensitivities of the ALL cell lines were not the same as those of the CML cell lines. These results suggest that a specific inhibitor of bcr/abl kinase could be an effective antileukemic agent against Ph-1-positive CML or ALL.

CC Cytology - Human 02508
Genetics - Human 03508
Biochemistry studies - General 10060

Biochemistry studies - proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Blood and hematopoietic agents 22008
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Development and Embryology - Morphogenesis 25508
Tissue culture, apparatus, methods and media 32500
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
HERBIMYCIN A; TYROSINE KINASE
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CHRONIC MYELOID LEUKEMIA CELLS; HERBIMYCIN A; KU-812 CELL LINES; PHILADELPHIA CHROMOSOME; TYROSINE KINASE INHIBITION
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
K-562: cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 70563-58-5 (HERBIMYCIN A)
80449-02-1 (TYROSINE KINASE)

L66 ANSWER 56 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:406664 BIOSIS Full-text
DOCUMENT NUMBER: PREV199396072389
TITLE: Cellular signaling events elicited by v-abl associated with growth factor independence in an interleukin-3-dependent cell line.
AUTHOR(S): Owen, P. Jane; Musk, Philip; Evans, Caroline A.; Whetton, Anthony D. [Reprint author]
CORPORATE SOURCE: Leukaemia Res. Fund Group, Dep. Biochem. and Applied Mol. Biol., Univ. Manchester Inst. Sci. and Technol., Sackville St., Manchester M60 1QD, United Kingdom, UK
SOURCE: Journal of Biological Chemistry, (1993) Vol. 268, No. 21, pp. 15696-15703.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Sep 1993
Last Updated on STN: 3 Jan 1995
AB A temperature-sensitive mutant of the v-abl oncoprotein has previously been shown to have markedly reduced tyrosine protein kinase activity in interleukin 3 (IL-3)-dependent cells grown at restrictive (39 degree C), compared to permissive (32 degree C) temperatures. Transfection of this mutant v-abl into

the IC2.9 cell line, generated the IC.DP subclone which was dependent on IL-3 for survival at 39 degree C, but not at 32 degree C. Furthermore, IC.DP cells cultured at 32 degree C exhibited IL-3-independent thymidine incorporation, which was not apparent at 39 degree C. Switching cells from the restrictive to the permissive temperature resulted in an increase in cellular inositol-1,4,5- trisphosphate, choline phosphate and diacylglycerol levels in the IC.DP cell line. These increases were only observed after a lag period of 4 h. Within 2 h of switching IC.DP cells previously maintained at 32 to 39 degree C, there was a significant decrease in all three metabolites. Temperature switches had no effect upon these metabolites in the parent IC2.9 cell line. Down-regulation of protein kinase C inhibited v-abl-stimulated DNA synthesis in IC.DP cells cultured at 32 degree C. IC.DP cells cultured at 32 degree C were found to have a constitutively activated Na+/H+ antiport, although this activation was inhibited by the down-modulation of protein kinase C. These data indicate a role for phospholipid hydrolysis and protein kinase C activation in V-ABL-mediated abrogation of IL-3 dependence.

CC Cytology - Animal 02506
Genetics - Animal 03506
Biophysics - Membrane phenomena 10508
Biophysics - Bioenergetics: electron transport and oxidative phosphorylation 10510
External effects - Temperature as a primary variable 10614
Enzymes - Physiological studies 10808
Metabolism - Energy and respiratory metabolism 13003
Metabolism - Lipids 13006
Metabolism - Minerals 13010
Blood - Blood cell studies 15004
Blood - Lymphatic tissue and reticuloendothelial system 15008
Endocrine - General 17002
Genetics of bacteria and viruses 31500
Virology - Animal host viruses 33506
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Metabolism

IT Chemicals & Biochemicals
PROTEIN KINASE C; SODIUM ION

IT Miscellaneous Descriptors
MEGAKARYOCYTE DIFFERENTIATION; PHORBOL MYRISTATE ACETATE; PROTEIN KINASE C ALPHA; SODIUM BUTYRATE

ORGN Classifier
Mammalia 85700
Super Taxa
Vertebrata; Chordata; Animalia
Organism Name
Mammalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
Retroviridae
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 147436-78-4 (PROTEIN KINASE C)
17341-25-2 (SODIUM ION)

L66 ANSWER 57 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:57983 BIOSIS Full-text
DOCUMENT NUMBER: PREV199497070983
TITLE: A C-terminal protein-binding domain in the retinoblastoma protein regulates nuclear c-Abl tyrosine kinase in the cell cycle.
AUTHOR(S): Welch, Peter J.; Wang, Jean Y. J.
CORPORATE SOURCE: Dep. Biol., Cent. Mol. Genet., Univ. Calif., San Diego, La Jolla, CA 92093-0116, USA
SOURCE: Cell, (1993) Vol. 75, No. 4, pp. 779-790.
CODEN: CELLB5. ISSN: 0092-8674.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Feb 1994
Last Updated on STN: 25 Mar 1994

AB The ubiquitously expressed c-Abl tyrosine kinase is localized to the nucleus and binds to DNA. The DNA binding activity is regulated by cdc2-mediated phosphorylation, suggesting a cell cycle function for c-Abl. Here we show that the tyrosine kinase activity of nuclear c-Abl is regulated in the cell cycle through a specific interaction with the retinoblastoma protein (RB). A domain In the C-terminus of RB, outside of the A/B pocket, binds to the ATP-binding lobe of the c-Abl tyrosine kinase, resulting in kinase inhibition. The RBc-Abl interaction is not affected by the viral oncoproteins that bind to RB. Hyperphosphorylation of RB correlates with release of c-Abl and activation of the tyrosine kinase in S phase cells. The nuclear c-Abl tyrosine kinase can enhance transcription, and this activity is inhibited by RB. Nuclear c-Abl is an S phase-activated tyrosine kinase that may participate directly in the regulation of transcription.

CC Microscopy - Cytology and cytochemistry 01054
Cytology - Animal 02506
Genetics - Animal 03506
Comparative biochemistry 10010
Biochemistry methods - General 10050
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Replication, transcription, translation 10300
Biophysics - Molecular properties and macromolecules 10506
Enzymes - Chemical and physical 10806
Enzymes - Physiological studies 10808
Anatomy and Histology - Microscopic and ultramicroscopic anatomy 11108
Physiology - General 12002
Pathology - General 12502
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Proteins, peptides and amino acids 13012
Metabolism - Nucleic acids, purines and pyrimidines 13014
Neoplasms - Carcinogens and carcinogenesis 24007
Tissue culture, apparatus, methods and media 32500

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Metabolism; Methods and Techniques; Molecular Genetics (Biochemistry and Molecular Biophysics); Morphology; Pathology; Physiology; Tumor Biology

IT Chemicals & Biochemicals
TYROSINE KINASE

IT Miscellaneous Descriptors

ANIMAL CELLS; ENZYMES; EXPRESSION; ONCOPROTEINS; PROTOONCOGENES; REGULATION; TRANSCRIPTION

ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
Animalia
Taxa Notes
Animals

RN 80449-02-1 (TYROSINE KINASE)

L66 ANSWER 58 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:478700 BIOSIS Full-text
DOCUMENT NUMBER: PREV199294110075; BA94:110075
TITLE: BENZOPYRANONES AND BENZOTHIOPYRANONES A CLASS OF TYROSINE PROTEIN KINASE INHIBITORS WITH SELECTIVITY FOR THE V-ABL KINASE.
AUTHOR(S): GEISSLER J F [Reprint author]; ROESEL J L; MEYER T; TRINKS U P; TRAXLER P; LYDON N B
CORPORATE SOURCE: PHARMACEUTICALS DIV, ONCOL VIROL RES DEP, CIBA-GEIGY LTD, K-125420, CH-4002 BASEL, SWITZ
SOURCE: Cancer Research, (1992) Vol. 52, No. 16, pp. 4492-4498.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Oct 1992
Last Updated on STN: 13 Dec 1992

AB Abelson murine leukemia virus is an acutely transforming replication-defective virus which encodes a transforming protein with tyrosine-specific protein kinase activity. A variety of benzopyranone and benzothiopyranone derivatives have been identified which selectively inhibit the v-abl tyrosine protein kinase with 50% inhibitory concentrations ranging from 1 to 30 μM. The most active derivative inhibited v-abl with a Ki value of 0.9 μM. Active derivatives showed selectivity for the v-abl tyrosine protein kinase relative to the epidermal growth factor receptor tyrosine protein kinase (50% inhibitory concentration > 100 μM). Protein kinase C and protein kinase A, two members of the serine/threonine protein kinase family, were not inhibited by benzopyranones or benzothiopyranones (50% inhibitory concentration > 100 μM). Kinetically, a representative derivative (compound 2) showed competitively with respect to ATP and noncompetitive behavior with respect to the exogenous peptide substrate. Autophosphorylation of p120v-abl and recombinant p70v-abl tyrosine protein kinases were also inhibited by benzopyranones and benzothipyranones in vitro. When tested in Abelson murine leukemia virus-transformed BALB/c cell, active benzopyranone and benzothiopyranone derivatives inhibited tyrosine phosphorylation of cellular proteins by the v-abl tyrosine protein kinase.

CC Cytology - Animal 02506
Genetics - Animal 03506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Carcinogens and carcinogenesis 24007
Virology - Animal host viruses 33506

IT Major Concepts

Cell Biology; Enzymology, Biochemistry and Molecular Biophysics); Genetics; **Microbiology**; Pharmacology; Tumor Biology

IT Miscellaneous Descriptors
MURINE LEUKEMIA **VIRUS** MOUSE ENZYME INHIBITOR-DRUG GENE ALTERATIONS CELLULAR TRANSFORMATION

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing **Viruses**; **Viruses**; Microorganisms
Taxa Notes
DNA and RNA Reverse Transcribing **Viruses**, Microorganisms, **Viruses**

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 80449-02-1 (TYROSINE PROTEIN KINASE)
9031-44-1 (KINASE)

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ACCESSION NUMBER: 1993:27721 BIOSIS Full-text
DOCUMENT NUMBER: PREV199395015921
TITLE: Oncogenic v-**Abl** tyrosine **kinase** can **inhibit** or stimulate growth, depending on the cell context.
AUTHOR(S): Renshaw, Mark W.; Kipreos, Edward T.; Albrecht, Michael R.; Wang, Jean Y. J. [Reprint author]
CORPORATE SOURCE: Dep. Biology Center Molecular Genetics, University California San Diego, 9500 Gilman Drive, La Jolla, Calif. 92093-0116, USA
SOURCE: EMBO (European Molecular Biology Organization) Journal, (1992) Vol. 11, No. 11, pp. 3941-3951.
CODEN: EMJODG. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Dec 1992
Last Updated on STN: 24 Dec 1992

AB The v-abl oncogene of Abelson murine leukemia **virus** (A-MuLV) induces two opposite phenotypes in NIH3T3 cells. In the majority of cells, v-abl causes a growth arrest at the G-1 phase of the cell cycle; while in a minority of cells, v-abl abrogates the requirement for growth factors Using temperature sensitive mutants, it can be demonstrated that v-**Abl** tyrosine **kinase** is requied for growth **inhibition** or stimulation. The two phenotypes are not caused by mutations or differences in the expression of v-Abl, but are dependent on the cell context. Two stable subclones of NIH3T3 cells have been isolated that exhibit similar morphology and growth characteristics. However, upon infection with A-MuLV, the 'positive' cells become serum- and anchorage-independent, whereas the 'negative' cells become arrested in G-1. The positive phenotype is dominant, shown by cell fusion, and treatment with 5-azacytidine converts the negative cells to the positive phenotype. Activation of v-Abl tyrosine kinase induces the serum-responsive genes in the positive but not in the negative cells. Transactivation of the c-fos promoter by v-Abl in transient assays is also restricted to the positive cells. These results show that v-Abl tyrosine kinase is not an obligatory activator of growth, but requires a permissive cellular context to manifest its mitogenic function.

CC Cytology - Animal 02506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Metabolism - Nucleic acids, purines and pyrimidines 13014
Nutrition - General studies, nutritional status and methods 13202
Blood - Blood and lymph studies 15002
Neoplasms - Carcinogens and carcinogenesis 24007
Development and Embryology - Morphogenesis 25508
Genetics of bacteria and viruses 31500
Tissue culture, apparatus, methods and media 32500
Medical and clinical microbiology - Virology 36006
IT Major Concepts
Cell Biology; Development; Genetics; Infection; Metabolism; Tumor Biology
IT Chemicals & Biochemicals
TYROSINE KINASE; 5-AZACYTIDINE
IT Miscellaneous Descriptors
GENE REGULATION; NIH-3T3 CELL LINE; PROMOTER TRANSACTIVATION; SERUM RESPONSIVE GENE; 5=AZACYTIDINE
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
murine
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
Abelson murine leukemia virus
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 80449-02-1 (TYROSINE KINASE)
320-67-2 (5-AZACYTIDINE)

L66 ANSWER 60 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:53600 BIOSIS Full-text
DOCUMENT NUMBER: PREV199395029902
TITLE: Synthesis and biological evaluation of a series of flavones designed as inhibitors of protein tyrosine kinases.
AUTHOR(S): Cunningham, Bernadette D. M.; Threadgill, Michael D. [Reprint author]; Groundwater, Paul W.; Dale, Ian L.; Hickman, John A.
CORPORATE SOURCE: Sch. Pharmacy Pharmacol., Univ. Bath, Claverton Down, Bath BA2 7AY, UK
SOURCE: Anti-Cancer Drug Design, (1992) Vol. 7, No. 5, pp. 365-384.
CODEN: ACDDEA. ISSN: 0266-9536.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jan 1993
Last Updated on STN: 14 Jan 1993
AB A series of flavones has been prepared, which are variously substituted in the 3,3',4',5 and 7 positions with halo-, alkoxy-, nitro-, amino-, hydroxy-,

acyloxy- and azido-groups, for evaluation of their cytotoxicity to ANN-1 cells (3T3 murine fibroblasts transformed with the Abelson murine leukaemia virus) which contain a tyrosine kinase. This cytotoxicity was compared to their non-transformed 3T3 counterparts. 3'-Amino-4'-methoxyflavone was the most cytotoxic compound (IC-50 = 1.6 mu-M) and was less inhibitory to the non-transformed parent 3T3 cell line (IC-50 = 8 mu-M). The compound was inactive at 50 mu-M in assays of the **inhibition** of the cell-associated **Abelson** protein tyrosine **kinase** but **inhibited** an epidermal growth factor (EGF) protein tyrosine kinase by 42% at 50 mu-M. Quercetin (3,3',4',5,7-pentahydroxyflavone) was the most potent **inhibitor** of the **Abelson** protein tyrosine **kinase** but showed no selective **inhibition** of the growth of ANN-1 cells compared to the parent 3T3 cell line. Different structure-activity relationships were observed between the results of the cytotoxicity assays and inhibition of protein tyrosine kinases. **Inhibitors** of the **Abelson** protein tyrosine **kinase** which were competitive with respect to ATP showed different potencies for inhibition of the EGF receptor kinases.

CC Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Enzymes - Physiological studies 10808
Endocrine - General 17002
Pharmacology - General 22002
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Pharmacology; Tumor Biology

IT Chemicals & Biochemicals
FLAVONES; PROTEIN TYROSINE KINASES; QUERCETIN; KINASE; ATP

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; ATP; CYTOTOXICITY; ENZYME INHIBITOR-DRUG; EPIDERMAL GROWTH FACTOR RECEPTOR KINASE; QUERCETIN; 3'=AMINO-4'-METHOXYFLAVONE

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 525-82-6D (FLAVONES)
80449-02-1D (PROTEIN TYROSINE KINASES)
117-39-5 (QUERCETIN)
9031-44-1 (KINASE)
56-65-5Q (ATP)
42530-29-0Q (ATP)
94587-45-8Q (ATP)
111839-44-2Q (ATP)
87805-51-4Q (ATP)

L66 ANSWER 61 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:282644 BIOSIS Full-text
DOCUMENT NUMBER: PREV199294007294; BA94:7294
TITLE: EFFECTS OF HERBIMYCIN A DERIVATIVES ON GROWTH AND DIFFERENTIATION OF K562 HUMAN LEUKEMIC CELLS.
AUTHOR(S): HONMA Y [Reprint author]; KASUKABE T; HOZUMI M; SHIBATA K;

OMURA S
CORPORATE SOURCE: 818 KOMURO INA-MACHI, KITAADACHI-GUN, SAITAMA-KEN 362, JPN
SOURCE: Anticancer Research, (1992) Vol. 12, No. 1, pp. 189-192.
CODEN: ANTRD4. ISSN: 0250-7005:
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jun 1992
Last Updated on STN: 10 Jun 1992

AB Herbimycin A, a specific tyrosine kinase inhibitor, induced erythroid differentiation of human myelogenous leukemia K562 cells with a high level of bcr/abl tyrosine kinase. Several derivatives of herbimycin A were synthesized and their effects on cell proliferation and differentiation of K562 cells were examined. Of the compounds tested, 19- allylaminoherbimycin A was the most effective in inducing differentiation of K562 cells. However, the parent compound was the most potent growth inhibitor, suggesting that chemical modification of herbimycin A reduces the growth-inhibiting activity. The sensitivities of K562 cells to herbimycin derivatives were different from those of a rat kidney cell line infected with Rous sarcoma **virus** (v-src), suggesting that bcr/abl kinase may differ in sensitivity from other tyrosine kinases. These results indicate that a specific **inhibitor** of bcr/ **abl kinase** could be an effective antitumour agent against chronic myelogenous leukemia.

CC Cytology - Human 02508
Biochemistry studies - General 10060
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Blood and hematopoietic agents 22008
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Development and Embryology - Morphogenesis 25508
Tissue culture, apparatus, methods and media 32500

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG TYROSINE KINASE INHIBITOR CHRONIC MYELOGENOUS LEUKEMIA

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 70563-58-5D (HERBIMYCIN A)
80449-02-1 (TYROSINE KINASE)

L66 ANSWER 62 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:456980 BIOSIS Full-text
DOCUMENT NUMBER: PREV199192101760; BA92:101760

TITLE: INDUCTION BY SOME PROTEIN KINASE INHIBITORS OF DIFFERENTIATION OF A MOUSE MEGAKARYOBLASTIC CELL LINE ESTABLISHED BY COINFECTION WITH ABELSON MURINE LEUKEMIA VIRUS AND RECOMBINANT SV-40 RETROVIRUS.

AUTHOR(S): HONMA Y [Reprint author]; OKABE-KADO J; KASUKABE T; HOZUMI M; KAJIGAYA S; SUDA T; MIURA Y

CORPORATE SOURCE: SAITAMA CANCER CENT, RES INST, INA-MACHI, KITAADACHI-GUN, SAITAMA-KEN 362, JPN

SOURCE: Cancer Research, (1991) Vol. 51, No. 17, pp. 4649-4655.
CODEN: CNREA8. ISSN: 0008-5472.

DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 11 Oct 1991
Last Updated on STN: 11 Oct 1991

AB Mouse C1 line cells are megakaryoblastic cells established by coinfection of Abelson murine leukemia **virus** and recombinant simian **virus** 40. We examined the effects of various compounds on growth and differentiation of these cells. Megakaryocytic differentiation of C1 cells was not induced by cytokines that stimulate megakaryocytic maturation of normal progenitor cells, such as interleukin 3 and 6 and granulocyte-macrophage colony-stimulating factor. However, the cells were induced to differentiate into megakaryocytes by treatment with some protein kinase inhibitors. The **inhibition** of v-**abl** tyrosine **kinase** activity preceded induction of differentiation of the cells treated with tyrosine kinase inhibitors such as genistein, herbimycin A, and erbstatin. Treatment of C1 cells with a v-abl antisense oligomer inhibited their proliferation and induced acetylcholinesterase activity, a typical marker of megakaryocytic differentiation. These results suggest that inhibition of v-abl function is associated with induction of megakaryocytic differentiation of C1 cells. Among the compounds tested, 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7), a potent inhibitor of cyclic nucleotide-dependent and Ca2+-phospholipid- dependent (protein kinase C) protein kinases, was the most potent inducer of differentiation of C1 cells. However, the differentiation-inducing effect of H-7 was unlikely to be mediated through inhibition of protein kinase C or cyclic nucleotide-dependent kinases, because other types of inhibitors of these kinases were not effective, and a protein kinase activator (phorbol ester) induced differentiation of C1 cells. Moreover, neither v-abl mRNA expression nor v-abl kinase activity in C1 cells was affected by treatment with H-7. These findings indicate that induction of megakaryocytic differentiation by H-7 is not related to **inhibition** of v-**abl kinase**, but rather to some novel function of H-7.

CC Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Enzymes - Chemical and physical 10806
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Endocrine - General 17002
Neoplasms - Carcinogens and carcinogenesis 24007
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Tumor Biology

IT Miscellaneous Descriptors
INTERLEUKIN GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR

ORGN Classifier
dsDNA **Viruses** 03100

Super Taxa
Viruses; Microorganisms
Taxa Notes
Double-Stranded DNA Viruses, Microorganisms, Viruses
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 9026-43-1Q (PROTEIN KINASE)
80449-02-1Q (PROTEIN KINASE)
134549-83-0Q (PROTEIN KINASE)
372092-80-3Q (PROTEIN KINASE)

L66 ANSWER 63 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:50877 BIOSIS Full-text
DOCUMENT NUMBER: PREV199191029158; BA91:29158
TITLE: **INHIBITION** OF **ABL** ONCOGENE TYROSINE **KINASE** INDUCES ERYTHROID DIFFERENTIATION OF HUMAN MYELOGENOUS LEUKEMIA K562 CELLS.
AUTHOR(S): HONMA Y [Reprint author]; OKABE-KADO J; KASUKABE T; HOZUMI M; UMEZAWA K
CORPORATE SOURCE: DEP CHEMOTHERAPY, SAITAMA CANCER CENT RES INST, INA-MACHI, SAITAMA 362, JPN
SOURCE: Japanese Journal of Cancer Research, (1990) Vol. 81, No. 11, pp. 1132-1136.
CODEN: JJCREP. ISSN: 0910-5050.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jan 1991
Last Updated on STN: 10 Jan 1991
AB The human chronic myelogenous leukemia cell line K562 expresses a structurally altered c-abl protein with tyrosine kinase activity. Erythroid differentiation of K562 cells was induced by tyrosine kinase inhibitors, but not by other kinase inhibitors. Treatment of K562 cells with 5'd(TACTGGCCGCTGAAGGGC)3', complementary to the second exon (codons 2 to 7) of c-abl mRNA, inhibited cell growth and induced benzidine-positive cells in a dose-dependent manner. However, exposure to the sense oligomer did not induce erythroid differentiation of the cells. These results suggest that **inhibition** of **abl** tyrosine **kinase** activity is closely related to induction of erythroid differentiation of K562 cells. A multidrug-resistant subline (K562R) was induced to undergo erythroid differentiation by tyrosine kinase inhibitors such as genistein or herbimycin A as effectively as the parent K562 cells were. Therefore, tyrosine kinase inhibitors might be useful as cancer chemotherapeutic agents against some multidrug-resistant leukemias having abnormally high activity of oncogene tyrosine kinase(s).
CC Cytology - Human 02508
Genetics - Human 03508

Biochemistry methods - Nucleic acids, purines and pyrimidines 10052
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Neoplasms - Carcinogens and carcinogenesis 24007
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Virology - Animal host viruses 33506

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Hematology (Human Medicine, Medical Sciences); **Microbiology**; Oncology (Human Medicine, Medical Sciences)

IT Miscellaneous Descriptors
ENZYME INHIBITOR AGENTS ANTINEOPLASTIC THERAPY MESSENGER RNA

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 80449-02-1 (TYROSINE KINASE)

L66 ANSWER 64 OF 88 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1984:343868 BIOSIS Full-text
DOCUMENT NUMBER: PREV198478080348; BA78:80348
TITLE: ONLY SITE DIRECTED ANTIBODIES REACTIVE WITH THE HIGHLY CONSERVED SRC HOMOLOGOUS REGION OF THE V-ABL PROTEIN NEUTRALIZE KINASE ACTIVITY.
AUTHOR(S): KONOPKA J B [Reprint author]; DAVIS R L; WATANABE S M; PONTICELLI A S; SCHIFF-MAKER L; ROSENBERG N; WITTE O N
CORPORATE SOURCE: DEP OF MICROBIOLOGY AND MOLECULAR BIOLOGY INSTITUTE, UNIV OF CALIFORNIA, LOS ANGELES, CALIFORNIA 90024, USA
SOURCE: Journal of Virology, (**1984**) Vol. 51, No. 1, pp. 223-232.
CODEN: JOVIAM. ISSN: 0022-538X.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Rabbit antisera specific for 6 regions of the v-abl protein were used to serologically characterize the Abelson murine leukemia **virus** tyrosine kinase. Chemically synthesized peptides corresponding to the predicted v-abl protein sequence and larger regions of the v-abl protein expressed as fusion proteins in **bacteria** [**Escherichia** coli] were used as immunogens. The specificity of each antiserum was confirmed by immunoprecipitation analysis with defined deletion mutants of Abelson murine leukemia **virus**. Several of these v-abl-specific antisera display much higher titer and avidities than serum harvested from mice bearing Abelson murine leukemia **virus**-induced tumors, previously the only source of anti-abl-specific serum. Two antisera were found to block the in vitro autophosphorylation of the v-abl protein as well as its ability to phosphorylate a peptide substrate. Examination of the sites against which the kinase-blocking antisera were prepared revealed that both are in close proximity to the in vivo sites of tyrosine phosphorylation, which fall within the region of high homology with v-src and other tyrosine kinases. Antisera directed against other regions of v- **abl** did not **inhibit kinase** activity.

CC Biochemistry methods - Proteins, peptides and amino acids 10054

Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Enzymes - General and comparative studies: coenzymes 10802
Enzymes - Methods 10804
Enzymes - Chemical and physical 10806
Metabolism - Proteins, peptides and amino acids 13012
Blood - Blood and lymph studies 15002
Neoplasms - Immunology 24003
Neoplasms - Carcinogens and carcinogenesis 24007
Physiology and biochemistry of bacteria 31000
Genetics of bacteria and viruses 31500
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Bacterial, viral and fungal 34504
Medical and clinical microbiology - Virology 36006

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); **Microbiology**

IT Miscellaneous Descriptors
ABELSON MURINE LEUKEMIA **VIRUS** ONCORNAVIRUS RABBIT MOUSE **ESCHERICHIA**-COLI **VIRAL** DELETION MUTANTS TYROSINE PHOSPHORYLATION/

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing **Viruses**; **Viruses**; Microorganisms
Taxa Notes
DNA and RNA Reverse Transcribing **Viruses**, Microorganisms, **Viruses**

ORGN Classifier
Enterobacteriaceae 06702
Super Taxa
Facultatively Anaerobic Gram-Negative Rods; Eubacteria; **Bacteria**; Microorganisms
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGN Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 9031-44-1 (KINASE)
60-18-4Q (TYROSINE)
556-03-6Q (TYROSINE)
55520-40-6Q (TYROSINE)

L66 ANSWER 65 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-30174 DRUGU P Full-text
TITLE: Efficacy of SCH66336, the farnesyl transferase inhibitor, against Gleevec-resistant BCR-ABL-positive cells.
AUTHOR: Nakajima A; Tauchi T; Sumi M; Bishop R W; Ohyashiki K
CORPORATE SOURCE: Univ.Tokyo-Med.; Schering-Plough
LOCATION: Tokyo, Jap.; Kenilworth, N.J., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (43, 93 Meet., 855, 2002) ISSN: 0197-016X
AVAIL. OF DOC.: 1st Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Combinations of SCH-66336 with second anti-leukemic agents were investigated, including Gleevec (imatinib mesilate; formerly CGP-57148-B; Novartis), daunorubicin (DNR), cytarabine (AraC) and etoposide (VP-16). The results indicated that SCH-66336 is a promising candidate for treating patients with Glivec-resistant Ph-positive leukemias and that combination of SCH-66336 and Glivec may be useful in an attempt to circumvent resistance. (conference abstract: 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2002).

L66 ANSWER 66 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-14232 DRUGU P B Full-text
TITLE: Chronic myelogenous leukemia CD34+ cells who increased sensitivity to pro-apoptotic stimuli which is reduced by imatinib.
AUTHOR: Holtz M; Forman S J; Bhatia R
LOCATION: Duarte, Cal., USA
SOURCE: Blood (100, No. 11, Pt. 2, 331b, 2002) 1 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Hematology and Bone Marrow Transplantation, City of Hope Cancer Center, Duarte, CA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In-vitro, imatinib mesylate (Gleevec) reduced otherwise high sensitivity to several proapoptotic stimuli in primary progenitor cells (CFC) from patients with chronic myelogenous leukemia (CML). Imatinib is a BCR/ ABL tyrosine **kinase inhibitor.** (conference abstract: 44th Annual Meeting of the American Society of Hematology, Philadelphia, Pennsylvania, USA, 2002).

L66 ANSWER 67 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-14230 DRUGU T Full-text
TITLE: Imatinib mesylate (Gleevec) suppresses Th1 cytokine production by CD4 T cells of patients with chronic myelogenous leukemia in cytogenetic remission.
AUTHOR: Lee B N; Talpaz M; Gao H; Shen D Y; Kantarjian H M; Reuben J M
CORPORATE SOURCE: Univ.Texas
LOCATION: Houston, Tex., USA
SOURCE: Blood (100, No. 11, Pt. 2, 330b, 2002)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Hematopathology, UT, M.D. Anderson Cancer Center, Houston, TX, U.S.A.
LANGUAGE: English

DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Unlike interferon-alpha, imatinib mesylate (STI-571, Gleevec) suppressed Th1 cytokine production by CD4+ T cells among 97 patients who achieved cytogenetic CR (CCR) of chronic myelogenous leukemia. Imatinib specifically **inhibits** tyrosine **kinase** activity of Bcr/**Abl**. (conference abstract: 44th Annual Meeting of the American Society of Hematology, Philadelphia, Pennsylvania, USA, 2002).

L66 ANSWER 68 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-45948 DRUGU T B Full-text
TITLE: Interferon-alpha-, but not STI571-induced remission from chronic myelogenous leukemia is associated with a myeloblastin-specific cytotoxic T-cell response potentially via induction of myeloblastin expression in monocytes.
AUTHOR: Burchert A; Woelfl S; Schmidt M; Brendel C; Beyer J; Hochhaus A; Neubauer A
CORPORATE SOURCE: Univ.Philipps-Marburg; Univ.Jena; Mologen; Univ.Heidelberg
LOCATION: Marburg, Jena, Berlin; Mannheim, Ger.
SOURCE: ; Proc.Am.Soc.Clin.Oncol. (21, Pt. 1, 274a, 2002)
CODEN: ; 7790
AVAIL. OF DOC.: Dept of Hematology/Oncology/Immunology, Philipps University Marburg, Marburg, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Distinct genetic and immunological regulations were associated with interferon (IFN)-alpha- and imatinib (STI-571)-induced remissions in patients with chronic myelogenous leukemia (CML). The Authors developed a model, explaining how IFN-alpha could trigger and/or maintain a CML-specific T-cell response via induction of myeloblastin or proteinase 3 (MBN) expression in antigen presenting monocytes. Long term outcome and prognostic significance of IFN-alpha-responses might therefore be distinct from remissions obtained with STI-571-therapy. (conference abstract: 38th Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, USA, 2002).

L66 ANSWER 69 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-43233 DRUGU T S Full-text
TITLE: STI571 (Gleevec/Glivec, imatinib) versus interferon IFN) + cytarabine as initial therapy for patients with CML: results of a randomized study.
AUTHOR: Druker B J
CORPORATE SOURCE: Univ.Oregon-Health-Sci.
LOCATION: Portland, Oreg., USA
SOURCE: ; Proc.Am.Soc.Clin.Oncol. (21, Pt. 1, 1a, 2002)
CODEN: ; 7790
AVAIL. OF DOC.: Oregon Health & Science University, Portland, OR, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB STI-571 (Gleevec/Glivec, imatinib), a specific **inhibitor** of the Bcr-**Abl** tyrosine **kinase**, is effective in late chronic, accelerated, and blast phases of chronic myeloid leukemia (CML). This open-label, multicenter, randomized, crossover trial evaluated STI-571 in comparison with interferon (IFN) + cytarabine in 1106 patients with newly diagnosed CML. Following a second

planned interim analysis of this study, the Independent Data Monitoring Board recommended that the data be disclosed early. Crossovers due to intolerance occurred in less than 1% of STI-571 cf. 19% of IFN-treated patients. STI-571 had significantly greater efficacy and was better tolerated than IFN as first line treatment of CML. Updated results were presented at the conference. (conference abstract: 38th Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, USA, 2002).

L66 ANSWER 70 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-09016 DRUGU P Full-text
TITLE: Restoration of sensitivity to STI571 in STI571-resistant chronic myeloid leukemia cells.
AUTHOR: Tipping A J; Mahon F X; Lagarde V; Goldman J M; Melo J V
LOCATION: London, U.K.; Bordeaux, Fr.
SOURCE: Blood (98, No. 13, 3864-67, 2001) 5 Fig. 11 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Dept of Haematology-ICSM, Hammersmith Hospital, Ducane Rd, London W12 0NN, England. (J.V.M.). (e-mail: j.melo@ic.ac.uk).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Long-term withdrawal of STI-571 (CGP-57148B, Novartis-Pharma) induced a decrease in survival and proliferation of LAMA84-resistant myeloid leukemia cells, but not of K562-r, KCL22-r, and Baf/BCR-ABL-r1 resistant cultures. LAMA84-resistant cells restored its sensitivity to STI-571 when maintained long-term off STI-571. Withdrawal of STI-571 from LAMA84-r led to a rapid increase in Bcr-Abl autophosphorylation and total phosphotyrosine content. Data suggest that if these results are equally applicable to primary chronic myeloid leukemia cells, then it is possible that selected patients who become refractory to STI-571 may benefit from a 2nd course of therapy after an interval off this inhibitor.

L66 ANSWER 71 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-15296 DRUGU T Full-text
TITLE: Activity of the **ABL-tyrosine kinase inhibitor** Glivec (STI-571) in Philadelphia chromosome positive acute lymphoblastic leukemia (PH+ALL) relapsing after allogeneic stem cell transplantation (allo-SCT).
AUTHOR: Ottman O G; Wassmann B; Pfeifer H; Sheuring U; Thiede C; Brueck P; Binckebank A; Atta J; Martin H; Gschaidmeier H
CORPORATE SOURCE: Univ.Frankfurt; Novartis
LOCATION: Frankfurt, Ger; Basle, Switz.
SOURCE: Blood (98, No. 11, Pt. 1, 589a-590a, 2001)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Dept of Hematology, J.W. Goethe University, Frankfurt, Germany. (11 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The effects of STI-571 (STI, Glivec, imatinib mesylate) were investigated in 20 patients with Philadelphia chromosome positive acute lymphoblastic leukemia (PH+ALL) relapsing after allogeneic stem cell transplantation (allo-SCT) in a clinical trial. STI was effective in inducing CR in these patients. In conclusion, STI is highly effective as initial treatment of relapsed PH+ALL subsequent to allo-SCT, with a favorable safety profile.

(conference abstract: 43rd Annual Meeting of the American Society of Hematology, Orlando, Florida, USA, 2001).

L66 ANSWER 72 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-41382 DRUGU B P Full-text
TITLE: Bcr-Abl inhibition as a modality of CML therapeutics.
AUTHOR: Buchdunger G; Matter A; Druker B J
CORPORATE SOURCE: Novartis; Univ.Oregon-Health-Sci.
LOCATION: Basle, Switz.; Portland, Oreg., USA
SOURCE: ; Biochim.Biophys.Acta Rev.Cancer (1551, No. 1, M11-M18, 2001) 5 Fig. 2 Tab. 37 Ref.
CODEN: ; 1841
AVAIL. OF DOC.: Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201, U.S.A. (B.J.D). (e- mail: drukerb@ohsu.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The Bcr-Abl inhibition as a modality of chronic myelogenous leukemia (CML) therapeutics is reviewed. The clinical features of CML, Bcr-Abl as a therapeutic target, medicinal chemistry program, in vitro and in vivo profile of ST-1571 (imatinib), clinical studies with ST-1571, induction of resistance to ST-1571, structural basis of ST-1571 specificity, future challenges and opportunities are discussed. In conclusion, ST-1571 is an example of a rotationally designed, molecularly targeted therapy based on the specific abnormality present in a human malignancy.

L66 ANSWER 73 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-26088 DRUGU P Full-text
TITLE: Synergistic activity of STI571 with gamma-irradiation and chemotherapeutic drugs.
AUTHOR: Topaly J; Zeller W J; Ho A D; Fruehauf S
CORPORATE SOURCE: Univ.Heidelberg; German-Cancer-Res.Inst.
LOCATION: Heidelberg, Ger.
SOURCE: J.Cancer Res.Clin.Oncol. (127, Suppl. 1, S79, 2001)
CODEN: JCROD7 ISSN: 0171-5216
AVAIL. OF DOC.: Department of Internal Medicine V, University of Heidelberg, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Combinations of the **ABL**-specific tyrosine **kinase inhibitor**, STI-571, with gamma-irradiation, cytarabine, etoposide or mitoxantrone showed synergistic effects on the inhibition of the growth of BV173 chronic myelogenous leukemia (CML) cells in-vitro. Combinations of STI-571 with ACNU (nimustine), busulfan, carboplatin, cladribin, gemcitabine, hydroxyurea, mafosfamide, methotrexate, taxotere, thiotepa, topotecane and treosulfan were less synergistic or merely additive. BCR-ABL-negative HL60, KG1a and normal CD34+ progenitor cells were not affected by STI-571. The data suggest that combinations of STI-571 with the synergistic compounds should be considered for clinical testing in chronic or advanced phase CML. (conference abstract: 11th Congress of the Division of Experimental Cancer Research of the German Cancer Society, Heidelberg, Germany, 2001).

L66 ANSWER 74 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-01320 DRUGU P Full-text
TITLE: Efficacy of STI571, an Abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against Bcr-Abl-positive cells.
AUTHOR: Thiesing J T; Ohno Jones S; Kolibaba K S; Druker B J
CORPORATE SOURCE: Univ.Oregon-Health-Sci.
LOCATION: Portland, Oreg., USA
SOURCE: Blood (96, No. 9, 3195-99, 2000) 3 Fig. 1 Tab. 26 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Division of Hematology and Medical Oncology, L592 Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201, U.S.A. (B.J.D.; e-mail: drukerb@ohsu.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The combination of STI-571 (Novartis) with interferon-alpha (IFN; Schering-Plough), daunorubicin (DNR; Bedford) and cytarabine (Ara-C; Pharmacia+Upjohn) showed additive or synergistic effects on the growth of human megakaryoblastic MO7e cells, MO7p210, which express Bcr-Abl and Bcr-Abl positive K562 cells, while the combination of STI-571 with hydroxyurea (HU; Sigma-Chemical) demonstrated antagonistic effects. Colony-forming assays using bone marrow or peripheral blood samples from 4 chronic myelogenous leukemia (CML) patients were performed. There was consistent inhibition of colony formation for all patients at each dose of STI-571, whereas there was significant interpatient variability with the different antileukemic agents. STI-571 in combination with IFN, DNR, Ara-C and HU produced substantial decreases in colony formation.

L66 ANSWER 75 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-43659 DRUGU P Full-text
TITLE: CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs.
AUTHOR: Fang G; Naekyung Kim C; Perkins C L; Ramadevi N; Winton E; Wittmann S; Bhalla K N
CORPORATE SOURCE: H.Lee.Moffitt-Cancer-Cent.; Univ.South-Florida; Univ.Emory
LOCATION: Tampa, Fla.; Atlanta, Ga., USA
SOURCE: Blood (96, No. 6, 2246-53, 2000) 7 Fig. 2 Tab. 48 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, MRC3E, Room 3056D, Tampa, FL 33612, USA. (e-mail: bhallakn@moffitt.usf.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The Bcr-Abl-specific tyrosine kinase inhibitor CGP-57148B (STI-571), citarabine (CA), doxorubicin (DR), etoposide (ET) and TNF-alpha were incubated with human Bcr-Abl-positive HL60/Bcr-Abl acute myeloid leukemia and chronic myeloid leukemia blast crisis K562 cells. Hemoglobin production was induced by the ectopic expression of Bcr-Abl. In HL-60/Bcr-Abl and K562 cells, nuclear factor kappaB activity contributed to the resistance to apoptosis due to TNF-alpha but not due to CA, ET or DR. CGP-57148B exposure increased hemoglobin levels and CD11b expression, altered intracellular levels of Bcr-Abl, Abl, Bcl-2, Bax and Apaf-1, inhibited Akt kinase activity and lowered XIAP and cIAP1 levels. CGP-57148B also inhibited NF-kappaB

activity and induced apoptosis. Combinations of CGP-57148B and antileukemic drugs may improve in-vivo efficacy.

L66 ANSWER 76 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-31338 DRUGU P Full-text
TITLE: Novel anti-Bcr-Abl strategies incorporating ST1571 (CGP57148B), arsenic trioxide (AT) and TRAIL (AP02L) against Bcr-Abl positive human leukemic cells.
AUTHOR: Perkins C; Ramadevi N; Porosnicu M; Fang G; Orlando M; Nguyen D; Bhalla K
CORPORATE SOURCE: Univ.Miami
LOCATION: Miami, Fla., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (41, 91 Meet., 389, 2000) ISSN: 0197-016X
AVAIL. OF DOC.: University of Miami, Miami, FL, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Novel anti-Bcr-Abl strategies incorporating ST-1571 (CGP-57148B), arsenic trioxide (AT) and TRAIL (APO2L; TNF-related apoptosis-inducing ligand) were evaluated against Bcr-Abl positive human leukemic cells. STI-571 and AT synergistically induced apoptosis of HL-60 and K562 cells. Co-treatment with STI-571 also significantly enhanced cytarabine (Ara-C, doxorubicin (DOX) and etoposide (VP16) induced apoptosis. TRAIL only induced apoptosis in the presence of STI-571. These findings indicate potential therapeutic anti-Bcr-Abl strategies incorporating novel agents, which target antiapoptotic oncoproteins and induce apoptotic signaling in Bcr-Abl positive leukemic cells. (conference abstract: 91st Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2000).

L66 ANSWER 77 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-38105 DRUGU P Full-text
TITLE: Molecular determinants of the antiapoptotic and antidifferentiating effects of Bcr-Abl kinase in human leukemic cells.
AUTHOR: Fang G; He J; Wittmann S; Jia T; Kim C N; Yalowich J C; Bhalla K
CORPORATE SOURCE: Univ.Emory; Univ.Pittsburgh
LOCATION: Atlanta, Ga; Pittsburgh, Pa., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (40, 90 Meet., 737, 1999) ISSN: 0197-016X
AVAIL. OF DOC.: Winship Cancer Center, Emory University School of Medicine, Atlanta, GA 30322, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The molecular determinants of the antiapoptotic and antidifferentiating effects of Bcr-Abl kinase were studied in human leukemic cells. Following treatment with high-dose Ara-C (HIDAC) or doxorubicin (Dox), both HL-60/Bcr-Abl and K562 cells failed to show caspase-8 and BID (cytosolic, proapoptotic BH3 domain containing protein) cleavage, cytosolic accumulation of cytochrome c (cyt c), caspase-3 activity and apoptosis. Treatment of HL60/Bcr-Abl and K562 cells with the Bcr-**Abl kinase inhibitor** CGP57148B increased low-dose cytarabine (LODAC)-induced Hb production and increased high-dose cytarabine (HIDAC) and doxorubicin (Dox)-induced apoptosis with concomitant increase in BID cleavage, cytosolic cyt c and caspase-3 activity. (conference abstract:

Philadelphia, Pennsylvania, USA, 1999).

L66 ANSWER 78 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-17289 DRUGU P B Full-text
TITLE: Novel anti-Bcr-Abl strategy consisting of arsenic trioxide and CGP57148B lowers Bcr-Abl levels and tyrosine kinase activity resulting in apoptosis and differentiation of Bcr-Abl positive human leukemia cells.
AUTHOR: Perkins C; Fang G; Orlando M; Porosnicu M; Kim C; Whittmann S; Wen J; Bhalla K
CORPORATE SOURCE: Univ.Miami-Sylvester-Compr.Cancer-Cent.
LOCATION: Miami, Fla., USA
SOURCE: Blood (94, No. 10, Pt. 1 Suppl. 1, 592a-593a, 1999)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Division of Clinical and Translational Research, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Effects of clinically achievable concentrations of arsenic trioxide (As2O3) and/or the Bcr-Abl tyrosine **kinase** (TK) specific **inhibitor** CGP-57148B (Novartis) on Bcr-Abl levels and activity as well as the differentiation status of human myeloid leukemia HL-60/Bcr-Abl and erythroleukemia K562 cells. CGP-57148B sensitized the cells to the apoptosis-inducing actions of cytarabine (Ara-C), doxorubicin (DOX) and etoposide (VP16). The data demonstrated that a treatment strategy which combines an agent that lowers Bcr-Abl levels with an agent that inhibits Bcr-Abl TK activity can potently induce differentiation and apoptosis of Bcr-Abl positive human leukemic cells. Further clinical evaluation of this strategy is warranted against drug refractory Bcr-Abl positive human leukemia. (conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).

L66 ANSWER 79 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-21431 DRUGU P Full-text
TITLE: Combination therapy of chronic myelogenous leukemia employing bcr/abl specific tyrosine **kinase** **inhibition.**
AUTHOR: Topaly J; Zeller W J; Ho A D; Fruehauf S
CORPORATE SOURCE: German-Cancer-Res.Cent.Heidelberg; Univ.Heidelberg
LOCATION: Heidelberg, Ger.
SOURCE: Blood (94, No. 10, Pt. 2 Suppl. 1, 281b, 1999) 1 Tab.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: German Cancer Research Center, Heidelberg, D-0200, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Effects of the selective **inhibitor** of bcr/abl tyrosine **kinase** (TK), CGP-57148B, alone and in combination with cytarabine (ara-C), hydroxyurea (HU), mafosfamide (Maf) and etoposide (VP-16), were investigated in-vitro against the bcr/abl +ve human CML cell lines BV173, K562, and EM-3 (all carrying p210BCR-ABL) and the bcr/abl -ve human leukemic cell lines HL-60 and KG1a. Combination of CGP-57148B with cytotoxic drugs selectively and synergistically increased their toxicity on bcr/abl+ cells and thus could be

used to fully exploit the therapeutic potential of the new bcr/abl TK inhibitor CGP-57148B. (conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).

L66 ANSWER 80 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-21409 DRUGU P Full-text
TITLE: Altered interferon-alpha responsiveness in K562 cells pretreated with **Abl**-tyrosine **kinase inhibitor** CGP57148B.
AUTHOR: Barteneva N; Stiouf I; Donato N; Kornblau S; Van N; Domain D; Talpaz M
CORPORATE SOURCE: Univ.Texas-Syst.M.D.Anderson-Cancer-Cent.
LOCATION: Houston, Tex., USA
SOURCE: Blood (94, No. 10, Pt. 2 Suppl. 1, 272b, 1999) 2 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: The University of Texas MD Anderson Cancer Center, Houston, TX, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In order to determine whether CGP-57148B affects sensitivity to interferon-alpha (IFN) in leukemic cells, the combination of these agents on K562 erythroleukemia cell growth and survival was evaluated. Pretreatment of K562 cells with the **Abl**-tyrosine **kinase inhibitor** CGP-57148B lowered the apoptotic threshold and significantly increased the sensitivity of these cells to the antitumor effects of IFN via a mechanism that is currently under investigation. (conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).

L66 ANSWER 81 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-11954 DRUGU P Full-text
TITLE: Efficacy of an **Abl** tyrosine **kinase inhibitor** in conjunction with other anti-neoplastic agents against Bcr-Abl positive cells.
AUTHOR: Thiesing J T; Ohno Jones S; Kolibaba K S; Druker B J
CORPORATE SOURCE: Univ.Oregon-Health-Sci.
LOCATION: Portland, Oreg., USA
SOURCE: Blood (94, No. 10, Pt. 1 Suppl. 1, 100a-101a, 1999)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: School of Medicine, Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, OR, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Combinations of STI-571 (CGP-57148B), a rationally designed **Abl** tyrosine **kinase inhibitor**, with other antileukemic agents: interferon-alpha (IFN), hydroxyurea (HU), daunorubicin (DNR) and cytarabine (Ara-C), were evaluated for activity against Bcr-Abl positive cells. Proliferation assays were performed using a human megakaryoblastic cell line (MO7e), a derivative engineered to express Bcr-Abl (MO7p210), and a Philadelphia chromosome-positive cell line derived from a chronic myelogenous leukemia (CML) blast crisis patient (K562). It appeared that combinations of STI-571 with IFN, DNR or Ara-C may be more useful than STI-571 alone in the treatment of CML. Phase II clinical trials of these combinations should be initiated.

(conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).

L66 ANSWER 82 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-21599 DRUGU P Full-text
TITLE: Herbimycin A sensitizes Philadelphia-positive leukaemia cells to apoptosis induction.
AUTHOR: Riordan F A; Bravery C A; Ray N; Borthwick N J; Akbar A; Hoffbrand A V; Wickremasinghe R G
CORPORATE SOURCE: Univ.London
LOCATION: London, U.K.
SOURCE: Br.J.Haematol. (97, Suppl. 1, 20, 1997)
CODEN: BJHEAL ISSN: 0007-1048
AVAIL. OF DOC.: Department of Haematology, Royal Free Hospital Medical School, London NW3 2QG, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB As the protein tyrosine kinase activity of the Philadelphia (Ph) chromosome-encoded bcr/abl oncoprotein abrogates the induction of apoptosis following treatment of Ph+ leukemia cells with DNA damaging agents, the Authors investigated the ability of the bcr/**abl** -selective **kinase inhibitor** herbimycin A (HMA) to enhance gamma irradiation- and etoposide-induced apoptosis in the CML cell-lines K562 and KCL 22 and in the Ph+ ALL line TOM 1. The findings demonstrated that the induction of nuclear apoptotic changes is inhibited in Ph+ cell-lines and that HMA treatment overcomes this block. Selective protein tyrosine kinase inhibitors may therefore be of value in securing the genetic death of Ph+ leukemia cells. (conference abstract).

L66 ANSWER 83 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-16544 DRUGU P S Full-text
TITLE: Treatment of Philadelphia-chromosome-positive human leukemia in SCID mouse model with herbimycin A, bcr-**abl** tyrosine **kinase** activity **inhibitor**.
AUTHOR: Honma Y; Matsuo Y; Hayashi Y; Omura S
CORPORATE SOURCE: Cancer-Cent.Res.Inst.Saitama; Hayashibara; Univ.Tokyo; Kitasato-Inst.
LOCATION: Saitama, Okayama; Tokyo, Jap.
SOURCE: Int.J.Cancer (60, No. 5, 685-88, 1995) 4 Fig. 3 Tab. 24 Ref.
CODEN: IJCNAW ISSN: 0020-7136
AVAIL. OF DOC.: Department of Chemotherapy, Saitama Center Research Institute, 818 Komura, Ina-machi, Saitama 362, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB I.p. and s.c. herbimycin A (HA), a bcr-**abl** tyrosine **kinase inhibitor**, prolonged the mean survival time of i.p. cyclophosphamide-treated mice inoculated with Philadelphia chromosome (Ph)-positive leukemia cells (NALM20, NALM24, SCMC-L2, UTPL2, K562 and KU812), but noth mice innoculated with Ph-negative cells (U937, HL60, BALL1 and HEL). HA caused no side-effects. I.p. HA was more effective the s.c. HA and prolonged the survival of leukemic mice in a dose-dependent manner. The SCID mouse-NALM20 human leukemia chimera would be a good experimental model for screening tyrosine kinase inhibitors as therapeutic agents against Ph-positive leukemias.

L66 ANSWER 84 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-19465 DRUGU B C M Full-text
TITLE: Paeciloquinones A, B, C, D, E and F: New potent inhibitors of protein tyrosine kinases produced by Paecilomyces carneus. I. Taxonomy, fermentation, isolation and biological activity.
AUTHOR: Petersen F; Fredenhagen A; Mett H; Lydon N B; Delmendo R; Jenny H B; Peter H H
CORPORATE SOURCE: CIBA-Geigy; Panlabs
LOCATION: Basel, Switz.; Bothell, Wash., USA
SOURCE: J.Antibiot. (48, No. 3, 191-98, 1995) 4 Fig. 1 Tab. 19 Ref.
CODEN: JANTAJ ISSN: 0021-8820
AVAIL. OF DOC.: Core Drug Discovery Technologies, Pharmaceutical Research, Ciba-Geigy Ltd., 4002 Basel, Switzerland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The taxonomy, fermentation, isolation and biological activity of paeciloquinones A, B, C, D, E and F were reported. Paeciloquinones inhibited EGF-R (epidermal growth factor receptor), c-src and v-abl protein tyrosine kinases enzymes with IC50 values in the uM range. Paeciloquinones A and C were potent and selective **inhibitors** of the v-**abl** protein tyrosine **kinase**. A methyl ester of paeciloquinone-B was also tested, and versiconol was used as a reference compound. Paeciloquinone-A had no **antimicrobial** activity against yeasts, fungi or **bacteria**.

L66 ANSWER 85 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-10168 DRUGU P B Full-text
TITLE: Tyrphostin-Induced **Inhibition** of p210bcr-**abl** Tyrosine **Kinase** Activity Induces K562 to Differentiate.
AUTHOR: Anafi M; Gazit A; Zehavi A; Ben Neriah Y; Levitzki A
CORPORATE SOURCE: Univ.Hebrew-Jerusalem; Univ.Hadassah
LOCATION: Jerusalem, Israel
SOURCE: Blood (82, No. 12, 3524-29, 1993) 5 Fig. 2 Tab. 30 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Department of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB 35 Tyrphostins, including AG-514, AG-568, AG-1112 and AG-775, representing different families of synthetic protein tyrosine kinase (PTK) blockers were studied for their ability to induce differentiation of K562 cells. Only AG-1112 and AG-568 inhibited the activity of p210bcr-abl PTK activity in intact K562 cells, and also induced erythroid differentiation, at below toxic concentrations. AG-1112 also blocked platelet derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) autophosphorylation in Swiss 3T3 cells, but at much higher concentrations than required for PTK inhibition. Irreversible inhibition of p210 by Herbimycin A was due to protein degradation. Only AG-568 induced differentiation of murine erythroleukemia cells (MEL) devoid of p210bcr-abl.

L66 ANSWER 86 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-46319 DRUGU B P Full-text
TITLE: Benzopyranones and Benzothiopyranones: A Class of Tyrosine

TITLE: Protein Kinase Inhibitors with Selectivity for the v-abl Kinase.
AUTHOR: Geissler J F; Roesel J L; Meyer T; Trinks W P; Traxler P; Lydon N B
CORPORATE SOURCE: CIBA-Geigy
LOCATION: Basle, Switzerland
SOURCE: Cancer Res. (52, No. 16, 4491-98, 1992) 3 Fig. 1 Tab. 41 Ref. CODEN: CNREA8 ISSN: 0008-5472
AVAIL. OF DOC.: Pharmaceuticals Division, Oncology and Virology Research Department, CIBA-Geigy Ltd., K-125.4.20 Basel, Switzerland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Acylaminobenzopyranone and benzothiopyranone derivatives (compounds 1-21) selectively **inhibited** v-**abl** tyrosine protein **kinase** (PK). Apigenin (Sigma-Chemical) but not genistein inhibited v-abl tyrosine PK, while flavone had marginal activity. PK A and PK C were not affected. A representative derivative was a competitive inhibitor with respect to ATP and was non-competitive with respect to exogenous peptide substrate. Autophosphorylation of p120 v-alb and recombinant p70 v-alb tyrosine PK were also inhibited by benzopyranones/ benzothiopyranones in-vitro. In Abelson murine leukemia **virus** BALB/c fibroblast cells, benzopyranone and benzothiopyranone derivatives inhibited tyrosine phosphorylation of cellular proteins by v-abl tyrosine PK. Structure-activity is discussed.

L66 ANSWER 87 OF 88 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-48127 DRUGU P Full-text
TITLE: Herbimycin A, an Inhibitor of Tyrosine Kinase Prolongs Survival of Mice Inoculated with Myeloid Leukemia C1 Cells with High Expression of v-abl Tyrosine Kinase.
AUTHOR: Honma Y; Hozumi M
LOCATION: Ina, Japan
SOURCE: Biomed.Pharmacother. (46, No. 5-7, 281, 1992) 3 Ref. CODEN: BIPHEX ISSN: 0753-3322
AVAIL. OF DOC.: Department of Chemotherapy, Saitama Cancer Center Research Institute, Ina, Saitama-362, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Herbimycin A (HA), genistein and erbstatin induced the mouse megakaryoblastic cell line C1 to differentiate into megakaryoctes. The **inhibition** of v-**abl** tyrosine **kinase** activity preceded induction of differentiation. Treatment of C1 cells with a v-abl antisense oligomer inhibited their proliferation and induced anticholinesterase activity. HA caused 50% inhibition at low doses of growth of C1 cells but at high doses scarcely affected the growth of the mouse leukemia cell line M1 or of normal bone marrow cells. HA increased survival of mice injected with C1, but not M1 cells. Results suggest that herbimycin A and/or related compounds may be useful for the treatment of some types of leukemia in which tyrosine kinase activity is implicated as a determinant of the oncogenic state. (congress abstract).

L66 ANSWER 88 OF 88 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-261041 [23] WPIX
DOC. NO. NON-CPI: N1998-205793
DOC. NO. CPI: C1998-081031
TITLE: Consolidated ligand comprising two ligands - for

TITLE: different binding domains on protein, used as diagnostic agent, for drug screening and therapeutically, has greater affinity and specificity than single ligands.

DERWENT CLASS: B04 D16 S03
INVENTOR(S): BARANY, G; COWBURN, D; XU, Q; ZHENG, J
PATENT ASSIGNEE(S): (MINU) UNIV MINNESOTA; (UYRQ) UNIV ROCKEFELLER
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9816638	A1	19980423	(199823)*	EN	58<--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP MX					
AU 9674324	A	19980511	(199837)		<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9816638	A1	WO 1996-US16495	19961016
AU 9674324	A	AU 1996-74324	19961016
		WO 1996-US16495	19961016

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9674324	A Based on	WO 9816638

PRIORITY APPLN. INFO: WO 1996-US16495 19961016

AB WO 9816638 A UPAB: 19980610
Consolidated ligand (A) comprises two ligands (I), for separate domains on a target protein (II), connected via a linker. It has greater affinity and/or specificity for the domains than either (I) alone.

Also claimed are:
(1) a nucleic acid (B) encoding (A);
(2) host cells transformed with (B);
(3) antibodies (Ab) for (A), and
(4) immortalised cell line that produces monoclonal Ab.

USE - (A) are used:
(i) to determine presence and activity of (II), e.g. for diagnosing or monitoring cellular conditions associated with (II), e.g. a gamma - globulinaemia, acquired immune deficiency syndrome, angiogenesis, breast (or other) cancer, diabetes, Lyme disease, osteoporosis or ulcerative colitis;
(ii) to detect binding sites for (A);
(iii) to test compounds (potential therapeutic agents) for ability to modulate activity of (I), or
(iv) to prevent and/or treat cellular disorders, i.e. as inhibitors or activators of (II).

Typically (A) directed against **Abelson** protein **kinase** (**Abl**) may **inhibit** chromosomal translocation, e.g. to potentiate anticancer drugs; to treat chronic **viral** hepatitis or hairy cell leukaemia, or as an adjuvant in interferon therapy.

Ab are used to identify (A)-expressing clones, and to detect and/or quantify (A).

(A) are administered by injection, typically at 0.1-20 (preferably 0.5-10) mg/kg/day.

ADVANTAGE - Since (A) have higher affinity and/or specificity, they can provide pharmaceutical activity where individual ligands can not. Dwg.0/0

INVENTOR SEARCH

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                 ANN M"/AU OR "PENDERGAST ANN MARIE"/AU OR "PENDERGAST ANNE
                 MARIE"/AU OR "PENDERGAST ANNMARIE"/AU)
L60          262 SEA ("BURTON E"/AU OR "BURTON E A"/AU OR "BURTON ELIABETH"/AU
                 OR "BURTON ELISABETH A"/AU OR "BURTON ELIZABETH"/AU OR "BURTON
                 ELIZABETH A"/AU OR "BURTON ELIZABETH ANN"/AU)
L61           17 SEA L59 AND L60
L62          499 SEA (L59 OR L60)
L64           20 SEA L62 AND (ABL OR ABELSON)(3A) KINAS?(5A)(INHIB? OR BLOCK?
                 OR ANTAG?)
L65           35 SEA L61 OR L64


=> d l65 ibib ab tot

L65  ANSWER 1 OF 35  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:742963  HCAPLUS  Full-text
DOCUMENT NUMBER:          145:227637
TITLE:                    The Caenorhabditis elegans ABL-1 tyrosine kinase is
                          required for Shigella flexneri pathogenesis
AUTHOR(S):                Burton, Elizabeth A.; Pendergast, Ann
                          Marie; Aballay, Alejandro
CORPORATE SOURCE:         Department of Molecular Genetics and Microbiology,
                          Duke University Medical Center, Durham, NC, 27710, USA
SOURCE:                   Applied and Environmental Microbiology (2006), 72(7),
                          5043-5051
                          CODEN: AEMIDF; ISSN: 0099-2240
PUBLISHER:                American Society for Microbiology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    Shigellosis is a diarrheal caused by the gram-neg. bacterium Shigella
      flexneri.  Following ingestion of the bacterium, S. flexneri interferes with
      innate immunity, establishes an infection within the human colon, and
      initiates an inflammatory response that results in destruction of the tissue
      lining the gut.  Examination of host cell factors required for S. flexneri
      pathogenesis in vivo has proven difficult due to limited host susceptibility.
      Here, the authors report the development of a pathogenesis system that
      involves the use of Caenorhabditis elegans as a model organism to study S.
      flexneri virulence determinants and host mols. required for pathogenesis.
      They show that S. flexneri-mediated killing of C. elegans correlates with
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bacterial accumulation in the intestinal tract of the animal. The S. flexneri virulence plasmid, which encodes a type III secretory system as well as various virulence determinants crucial for pathogenesis in mammalian systems, was found to be required for maximal C. elegans killing. Addnl., the authors demonstrate that ABL-1, the C. elegans homolog of the mammalian c-Abl nonreceptor tyrosine kinase ABL1, is required for S. flexneri pathogenesis in nematodes. These data demonstrate the feasibility of using C. elegans to study S. flexneri pathogenesis in vivo and provide insight into host factors that contribute to S. flexneri pathogenesis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 2 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1111095 HCAPLUS Full-text
DOCUMENT NUMBER: 144:3190
TITLE: Abl kinases regulate actin comet tail elongation via an N-WASP-dependent pathway
AUTHOR(S): **Burton, Elizabeth A.**; Oliver, Timothy N.; **Pendergast, Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Molecular and Cellular Biology (2005), 25(20), 8834-8843
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Microbial pathogens have evolved diverse strategies to modulate the host cell cytoskeleton to achieve a productive infection and have proven instrumental for unraveling the mol. machinery that regulates actin polymerization Here we uncover a mechanism for Shigella flexneri-induced actin comet tail elongation that links Abl family kinases to N-WASP-dependent actin polymerization We show that the Abl kinases are required for Shigella actin comet tail formation, maximal intracellular motility, and cell-to-cell spread. Abl phosphorylates N-WASP, a host cell protein required for actin comet tail formation, and mutation of the Abl phosphorylation sites on N-WASP impairs comet tail elongation. Furthermore, we show that defective comet tail formation in cells lacking Abl kinases is rescued by activated forms of N-WASP. These data demonstrate for the first time that the Abl kinases play a role in the intracellular motility and intercellular dissemination of Shigella and uncover a new role for Abl kinases in the regulation of pathogen motility.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:16965 HCAPLUS Full-text
DOCUMENT NUMBER: 142:107361
TITLE: Method of blocking pathogen infection
INVENTOR(S): **Pendergast, Ann Marie**; **Burton, Elizabeth A.**
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 20050003377 A1 20050106 US 2003-734582 2003-1215
PRIORITY APPLN. INFO.: US 2002-432989P P 20021213
US 2003-507088P P 20031001

AB The present invention relates, in general, to pathogens and, in particular, to a method of blocking pathogen infection and to a method of identifying agents suitable for use in such a method.

L65 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:883751 HCAPLUS Full-text
DOCUMENT NUMBER: 141:153621
TITLE: Abl tyrosine kinases are required for infection by Shigella flexneri. [Erratum to document cited in CA140:056225]
AUTHOR(S): **Burton, Elizabeth A.**; Plattner, Rina; **Pendergast, Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: EMBO Journal (2003), 22(21), 5962
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A statement which should appear at the end of the legend to Figure 2B is as follows: "Fold uptake was normalized sep. for each of the three indicated cell types by comparison of bacterial internalization in the absence or presence of STI571. On average, uptake of S. flexneri 2457T by the Null cells was .apprx.5-fold lower than that by the Abl/Arg cells when normalization was performed across cell types.".

L65 ANSWER 5 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:824841 HCAPLUS Full-text
DOCUMENT NUMBER: 140:56225
TITLE: Abl tyrosine kinases are required for infection by Shigella flexneri
AUTHOR(S): **Burton, Elizabeth A.**; Plattner, Rina; **Pendergast, Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: EMBO Journal (2003), 22(20), 5471-5479
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Infection by the opportunistic bacterial pathogen Shigella flexneri stimulates tyrosine phosphorylation of host cell proteins, but the kinases involved and their effects on the regulation of cell signaling pathways during bacterial entry remain largely undefined. Here, we demonstrate a requirement for the Abl family of tyrosine kinases during Shigella internalization. Family members Abl and Arg are catalytically activated upon Shigella infection, accumulate at the site of bacterial entry, and are required for efficient bacterial uptake, as internalization is blocked upon targeted deletion of these kinases or treatment with a specific pharmacol. inhibitor. We identify the adapter protein Crk as a target for Abl kinases during Shigella uptake, and show that a phosphorylation- deficient Crk mutant significantly inhibits bacterial uptake. Moreover, we define a novel signaling pathway activated during Shigella entry that links Abl kinase phosphorylation of Crk to activation of the Rho family GTPases Rac and Cdc42. Together, these findings reveal a new role for the Abl kinases, and suggest a novel approach to

treatment of Shigella infections through inhibition of host cell signaling pathways.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:251855 HCAPLUS Full-text
DOCUMENT NUMBER: 139:160299
TITLE: A new link between the c-Abl tyrosine kinase and phosphoinositide signalling through PLC-γ1
AUTHOR(S): Plattner, Rina; Irvin, Brenda J.; Guo, Shuling; Blackburn, Kevin; Kazlauskas, Andrius; Abraham, Robert T.; York, John D.; **Pendergast, Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Nature Cell Biology (2003), 5(4), 309-319
CODEN: NCBIFN; ISSN: 1465-7392
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The c-Abl tyrosine (Tyr) kinase is activated after platelet-derived-growth factor receptor (PDGFR) stimulation in a manner that is partially dependent on Src kinase activity. However, the activity of Src kinases alone is not sufficient for activation of c-Abl by PDGFR. Here we show that functional phospholipase C-γ1 (PLC-γ1) is required for c-Abl activation by PDGFR. Decreasing cellular levels of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) by PLC-γ1-mediated hydrolysis or dephosphorylation by an inositol polyphosphate 5-phosphatase (Inp54) results in increased Abl kinase activity. C-Abl functions downstream of PLC-γ1, as expression of **kinase-inactive c-Abl blocks** PLC-γ1-induced chemotaxis towards PDGF-BB. PLC-γ1 and c-Abl form a complex in cells that is enhanced by PDGF stimulation. After activation, c-Abl phosphorylates PLC-γ1 and neg. modulates its function in vivo. These findings uncover a newly discovered functional interdependence between non-receptor Tyr kinase and lipid signaling pathways.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:948109 HCAPLUS Full-text
DOCUMENT NUMBER: 138:218530
TITLE: The Abl family kinases: mechanisms of regulation and signaling
AUTHOR(S): **Pendergast, Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Advances in Cancer Research (2002), 85, 51-100, 2 plates
CODEN: ACRSAJ; ISSN: 0065-230X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review focuses on the regulation and signaling of the Abl and Arg tyrosine kinases. It discusses the recent advances in the elucidation of the mechanisms that activate and **inhibit Abl kinase** activity, the identification of protein targets of the Abl kinases, the phenotypic consequences of inactivating Abl function in flies and mice, and the roles of Abl kinases in cell growth, survival, stress responses, and cytoskeletal processes. (c) 2002 Academic Press.

REFERENCE COUNT: 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:265511 HCAPLUS Full-text
DOCUMENT NUMBER: 129:26463
TITLE: Protein tyrosine phosphatase 1B antagonizes signalling by oncoprotein tyrosine kinase p210 bcr-abl in vivo
AUTHOR(S): Lamontagne, Kenneth R., Jr.; Flint, Andrew J.; Franza, B. Robert, Jr.; Pendergast, Ann Marie; Tonks, Nicholas K.
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 11724-2208, USA
SOURCE: Molecular and Cellular Biology (1998), 18(5), 2965-2975
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The p210 bcr-abl protein tyrosine kinase (PTK) appears to be directly responsible for the initial manifestations of chronic myelogenous leukemia (CML). In contrast to the extensive characterization of the PTK and its effects on cell function, relatively little is known about the nature of the protein tyrosine phosphatases (PTPs) that may modulate p210 bcr-abl-induced signaling. In this study, we have demonstrated that expression of PTP1B is enhanced specifically in various cells expressing p210 bcr-abl, including a cell line derived from a patient with CML. This effect on expression of PTP1B required the kinase activity of p210 bcr-abl and occurred rapidly, concomitant with maximal activation of a temperature-sensitive mutant of the PTK. The effect is apparently specific for PTP1B since, among several PTPs tested, we detected no change in the levels of TCPTP, the closest relative of PTP1B. We have developed a strategy for identification of physiol. substrates of individual PTPs which utilizes substrate-trapping mutant forms of the enzymes that retain the ability to bind to substrate but fail to catalyze efficient dephosphorylation. We have observed association between a substrate-trapping mutant of PTP1B (PTP1B-D181A) and p210 bcr-abl, but not v-Abl, in a cellular context. Consistent with the trapping data, we observed dephosphorylation of p210 bcr-abl, but not v-Abl, by PTP1B in vivo. We have demonstrated that PTP1B inhibited binding of the adapter protein Grb2 to p210 bcr-abl and suppressed p210 bcr-abl-induced transcriptional activation that is dependent on Ras. These results illustrate selectivity in the effects of PTPs in a cellular context and suggest that PTP1B may function as a specific, neg. regulator of p210 bcr-abl signaling in vivo.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:81633 HCAPLUS Full-text
DOCUMENT NUMBER: 126:155808
TITLE: The BCR-ABL tyrosine kinase inhibits apoptosis by activating a Ras-dependent signaling pathway
AUTHOR(S): Cortez, David; Stoica, Gerald; Pierce, Jacalyn; Pendergast, Ann Marie
CORPORATE SOURCE: Department Molecular Cancer Biology, Duke University Medical Cancer, Durham, NC, 27710, USA
SOURCE: Oncogene (1996), 13(12), 2589-2594
CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BCR-ABL is a deregulated tyrosine kinase that is expressed in Philadelphia chromosome (Ph1) pos. human leukemias. When expressed in hematopoietic cells, BCR-ABL causes cytokine independent proliferation, induces tumorigenic growth and prevents apoptosis in response to cytokine deprivation or DNA damage. One mechanism by which BCR-ABL signals in cells is by activating the small guanine nucleotide binding protein Ras. BCR-ABL-transformed cells have constitutively high levels of active, GTP-bound Ras. Here the authors use 32D cells that inducibly express a dominant neg. Ras protein to define the Ras requirements in BCR-ABL-transformed cells. Dominant neg. Ras inhibits BCR-ABL-mediated Ras activation, and induces cell death by an apoptotic mechanism. Therefore, BCR-ABL inhibits apoptosis through activation of a Ras-dependent signaling pathway.

L65 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:962584 HCAPLUS Full-text
DOCUMENT NUMBER: 124:6024
TITLE: Mutant forms of growth factor-binding protein-2 reverse BCR-ABL-induced transformation
AUTHOR(S): Gishizky, Mikhail L.; Cortez, David; **Pendergast, Ann Marie**
CORPORATE SOURCE: Dep. Hematol./Oncol., SUGEN, Inc., Redwood City, CA, 94063, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(24), 10889-93
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Growth factor-binding protein 2 (Grb2) is an adaptor protein that links tyrosine kinases to Ras. BCR-ABL is a tyrosine kinase oncoprotein that is implicated in the pathogenesis of Philadelphia chromosome (Ph1)-pos. leukemias. Grb2 forms a complex with BCR-ABL and the nucleotide exchange factor Sos that leads to the activation of the Ras protooncogene. In this report the authors demonstrate that Grb2 mutant proteins lacking N- or C-terminal Src homol. SH3 domains suppress BCR-ABL-induced Ras activation and reverse the oncogenic phenotype. The Grb2 SH3-deletion mutant proteins bind to BCR-ABL and do not impair tyrosine kinase activity. Expression of the Grb2 SH3-deletion mutant proteins in BCR-ABL-transformed Rat-1 fibroblasts and in the human Ph1-pos. leukemic cell line K562 inhibits their ability to grow as foci in soft agar and form tumors in nude mice. Furthermore, expression of the Grb2 SH3-deletion mutants in K562 cells induced their differentiation. Because Ras plays an important role in signaling by receptor and non-receptor tyrosine kinases, the use of interfering mutant Grb2 proteins may be applied to block the proliferation of other cancers that depend in part on activated tyrosine kinases for growth.

L65 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:489691 HCAPLUS Full-text
DOCUMENT NUMBER: 115:89691
TITLE: Evidence for regulation of the human **ABL** tyrosine **kinase** by a cellular **inhibitor**
AUTHOR(S): **Pendergast, Ann Marie**; Muller, Alexander J.; Havlik, Marie H.; Clark, Robin; McCormick, Frank; Witte, Owen N.

CORPORATE SOURCE: Mol. Biol. Inst., Univ. California, Los Angeles, CA, 90024, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1991), 88(13), 5927-31
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphotyrosine cannot be detected on normal human ABL protein-tyrosine kinases, but activated oncogenic forms of the human ABL protein are phosphorylated on tyrosine in vivo. Activation of ABL can occur by substitution of the ABL 1st exon with breakpoint cluster region (BCR) sequences or by deletion of the noncatalytic SH3 (src homol. region 3) domain. An alternative mode for the activation of the ABL kinases is hyperexpression at >500-fold over endogenous levels. This is not a consequence of transphosphorylation of the hyperexpressed ABL mols. ABL proteins translated in vitro lack phosphotyrosine, but tyrosine kinase activity is uncovered after immunopptn. and removal of lysate components. The rates of dephosphorylation of ABL and BCR-ABL fusion protein by phosphotyrosine-specific phosphatases are approx. the same. Apparently, inhibition of ABL activity is reversible and a cellular component interacts noncovalently with ABL to inhibit its autophosphorylation.

L65 ANSWER 12 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2006400664 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16820504
TITLE: The Caenorhabditis elegans ABL-1 tyrosine kinase is required for Shigella flexneri pathogenesis.
AUTHOR: **Burton Elizabeth A; Pendergast Ann Marie** ; Aballay Alejandro
CORPORATE SOURCE: Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC 27710, USA.
CONTRACT NUMBER: AI065641 (NIAID)
CA009111-27 (NCI)
CA70940 (NCI)
GM62375 (NIGMS)
GM70977 (NIGMS)
SOURCE: Applied and environmental microbiology, (2006 Jul) Vol. 72, No. 7, pp. 5043-51.
Journal code: 7605801. ISSN: 0099-2240.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200609
ENTRY DATE: Entered STN: 6 Jul 2006
Last Updated on STN: 6 Sep 2006
Entered Medline: 5 Sep 2006

AB Shigellosis is a diarrheal disease caused by the gram-negative bacterium Shigella flexneri. Following ingestion of the bacterium, S. flexneri interferes with innate immunity, establishes an infection within the human colon, and initiates an inflammatory response that results in destruction of the tissue lining the gut. Examination of host cell factors required for S. flexneri pathogenesis in vivo has proven difficult due to limited host susceptibility. Here we report the development of a pathogenesis system that involves the use of Caenorhabditis elegans as a model organism to study S. flexneri virulence determinants and host molecules required for pathogenesis. We show that S. flexneri-mediated killing of C. elegans correlates with bacterial accumulation in the intestinal tract of the animal. The S. flexneri virulence plasmid, which encodes a type III secretory system as well as

various virulence determinants crucial for pathogenesis in mammalian systems, was found to be required for maximal C. elegans killing. Additionally, we demonstrate that ABL-1, the C. elegans homolog of the mammalian c-Abl nonreceptor tyrosine kinase ABL1, is required for S. flexneri pathogenesis in nematodes. These data demonstrate the feasibility of using C. elegans to study S. flexneri pathogenesis in vivo and provide insight into host factors that contribute to S. flexneri pathogenesis.

L65 ANSWER 13 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2005525258 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16199863
TITLE: Abl kinases regulate actin comet tail elongation via an N-WASP-dependent pathway.
AUTHOR: **Burton Elizabeth A**; Oliver Timothy N; **Pendergast Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA.
CONTRACT NUMBER: CA009111-27 (NCI)
CA70940 (NCI)
GM62375 (NIGMS)
SOURCE: Molecular and cellular biology, (2005 Oct) Vol. 25, No. 20, pp. 8834-43.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200511
ENTRY DATE: Entered STN: 4 Oct 2005
Last Updated on STN: 15 Dec 2005
Entered Medline: 21 Nov 2005

AB Microbial pathogens have evolved diverse strategies to modulate the host cell cytoskeleton to achieve a productive infection and have proven instrumental for unraveling the molecular machinery that regulates actin polymerization. Here we uncover a mechanism for Shigella flexneri-induced actin comet tail elongation that links Abl family kinases to N-WASP-dependent actin polymerization. We show that the Abl kinases are required for Shigella actin comet tail formation, maximal intracellular motility, and cell-to-cell spread. Abl phosphorylates N-WASP, a host cell protein required for actin comet tail formation, and mutation of the Abl phosphorylation sites on N-WASP impairs comet tail elongation. Furthermore, we show that defective comet tail formation in cells lacking Abl kinases is rescued by activated forms of N-WASP. These data demonstrate for the first time that the Abl kinases play a role in the intracellular motility and intercellular dissemination of Shigella and uncover a new role for Abl kinases in the regulation of pathogen motility.

L65 ANSWER 14 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003470132 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14532119
TITLE: Abl tyrosine kinases are required for infection by Shigella flexneri.
AUTHOR: **Burton Elizabeth A**; Plattner Rina; **Pendergast Ann Marie**
CORPORATE SOURCE: Duke University Medical Center, Department of Pharmacology and Cancer Biology, Durham, NC 27710, USA.
CONTRACT NUMBER: CA70940 (NCI)
GM62375 (NIGMS)
SOURCE: The EMBO journal, (2003 Oct 15) Vol. 22, No. 20, pp.

- 5471-9.
Journal code: 820866. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 9 Oct 2003
Last Updated on STN: 10 Jan 2004
Entered Medline: 9 Jan 2004

AB Infection by the opportunistic bacterial pathogen Shigella flexneri stimulates tyrosine phosphorylation of host cell proteins, but the kinases involved and their effects on the regulation of cell signaling pathways during bacterial entry remain largely undefined. Here, we demonstrate a requirement for the Abl family of tyrosine kinases during Shigella internalization. Family members Abl and Arg are catalytically activated upon Shigella infection, accumulate at the site of bacterial entry, and are required for efficient bacterial uptake, as internalization is blocked upon targeted deletion of these kinases or treatment with a specific pharmacological inhibitor. We identify the adapter protein Crk as a target for Abl kinases during Shigella uptake, and show that a phosphorylation-deficient Crk mutant significantly inhibits bacterial uptake. Moreover, we define a novel signaling pathway activated during Shigella entry that links Abl kinase phosphorylation of Crk to activation of the Rho family GTPases Rac and Cdc42. Together, these findings reveal a new role for the Abl kinases, and suggest a novel approach to treatment of Shigella infections through inhibition of host cell signaling pathways.

L65 ANSWER 15 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003152284 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12652307
TITLE: A new link between the c-Abl tyrosine kinase and phosphoinositide signalling through PLC-gamma1.
AUTHOR: Plattner Rina; Irvin Brenda J; Guo Shuling; Blackburn Kevin; Kazlauskas Andrius; Abraham Robert T; York John D; **Pendergast Ann Marie**
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology Duke University Medical Center Durham, NC 27710, USA.
CONTRACT NUMBER: CA09111-25 (NCI)
CA70940 (NCI)
GM62375 (NIGMS)
SOURCE: Nature cell biology, (2003 Apr) Vol. 5, No. 4, pp. 309-19.
Journal code: 100890575. ISSN: 1465-7392.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 2 Apr 2003
Last Updated on STN: 17 May 2003
Entered Medline: 16 May 2003

AB The c-Abl tyrosine (Tyr) kinase is activated after platelet-derived-growth factor receptor (PDGFR) stimulation in a manner that is partially dependent on Src kinase activity. However, the activity of Src kinases alone is not sufficient for activation of c-Abl by PDGFR. Here we show that functional phospholipase C-gamma1 (PLC-gamma1) is required for c-Abl activation by PDGFR. Decreasing cellular levels of phosphatidylinositol- 4,5-bisphosphate (PtdIns(4,5)P2) by PLC-gamma1-mediated hydrolysis or dephosphorylation by an inositol polyphosphate 5-phosphatase (Inp54) results in increased Abl kinase

activity. c-Abl functions downstream of PLC-gamma1, as expression of kinase-inactive c-**Abl** blocks PLC-gamma1-induced chemotaxis towards PDGF-BB. PLC-gamma1 and c-Abl form a complex in cells that is enhanced by PDGF stimulation. After activation, c-Abl phosphorylates PLC-gamma1 and negatively modulates its function in vivo. These findings uncover a newly discovered functional interdependence between non-receptor Tyr kinase and lipid signalling pathways.

L65 ANSWER 16 OF 35 MEDLINE on STN
ACCESSION NUMBER: 97152549 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9000132
TITLE: The BCR-**ABL** tyrosine **kinase** **inhibits** apoptosis by activating a Ras-dependent signaling pathway.
AUTHOR: Cortez D; Stoica G; Pierce J H; **Pendergast A M**
CORPORATE SOURCE: Department of Molecular Cancer Biology, Duke University Medical Center, Durham, North Carolina 27710, USA.
CONTRACT NUMBER: CA61033 (NCI)
SOURCE: Oncogene, (1996 Dec 19) Vol. 13, No. 12, pp. 2589-94.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 27 Feb 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 11 Feb 1997

AB BCR-ABL is a deregulated tyrosine kinase that is expressed in Philadelphia chromosome (Ph1) positive human leukemias. When expressed in hematopoietic cells, BCR-ABL causes cytokine independent proliferation, induces tumorigenic growth and prevents apoptosis in response to cytokine deprivation or DNA damage. One mechanism by which BCR-ABL signals in cells is by activating the small guanine nucleotide binding protein Ras. BCR-ABL-transformed cells have constitutively high levels of active, GTP-bound Ras. Here we use 32D cells that inducibly express a dominant negative Ras protein to define the Ras requirements in BCR-ABL-transformed cells. Dominant negative Ras inhibits BCR-ABL-mediated Ras activation, and induces cell death by an apoptotic mechanism. Therefore, BCR-ABL inhibits apoptosis through activation of a Ras-dependent signaling pathway.

L65 ANSWER 17 OF 35 MEDLINE on STN
ACCESSION NUMBER: 91288576 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1712111
TITLE: Evidence for regulation of the human **ABL** tyrosine **kinase** by a cellular **inhibitor.**
AUTHOR: **Pendergast A M**; Muller A J; Havlik M H; Clark R; McCormick F; Witte O N
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, University of California, Los Angeles 90024.
CONTRACT NUMBER: GM07185 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1991 Jul 1) Vol. 88, No. 13, pp. 5927-31.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 25 Aug 1991
Last Updated on STN: 29 Jan 1996
Entered Medline: 2 Aug 1991

AB Phosphotyrosine cannot be detected on normal human ABL protein-tyrosine kinases, but activated oncogenic forms of the human ABL protein are phosphorylated on tyrosine in vivo. Activation of ABL can occur by substitution of the ABL first exon with breakpoint cluster region (BCR) sequences or by deletion of the noncatalytic SH3 (src homology region 3) domain. An alternative mode for the activation of the ABL kinases is hyperexpression at greater than 500-fold over endogenous levels. This is not a consequence of transphosphorylation of the hyperexpressed ABL molecules. ABL proteins translated in vitro lack phosphotyrosine, but tyrosine kinase activity is uncovered after immunoprecipitation and removal of lysate components. The rates of dephosphorylation of ABL and BCR-ABL fusion protein by phosphotyrosine-specific phosphatases are approximately the same. These combined results indicate that inhibition of ABL activity is reversible and suggest that a cellular component interacts noncovalently with ABL to inhibit its autophosphorylation.

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ACCESSION NUMBER: 2006343699 EMBASE Full-text
TITLE: The Caenorhabditis elegans ABL-1 tyrosine kinase is required for Shigella flexneri pathogenesis.
AUTHOR: **Burton E.A.**; **Pendergast A.M.**; Aballay A.
CORPORATE SOURCE: A.M. Pendergast, Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, United States. pende014@mc.duke.edu
SOURCE: Applied and Environmental Microbiology, (2006) Vol. 72, No. 7, pp. 5043-5051. .
Refs: 42
ISSN: 0099-2240 CODEN: AEMIDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2006
Last Updated on STN: 10 Aug 2006

AB Shigellosis is a diarrheal disease caused by the gram-negative bacterium Shigella flexneri. Following ingestion of the bacterium, S. flexneri interferes with innate immunity, establishes an infection within the human colon, and initiates an inflammatory response that results in destruction of the tissue lining the gut. Examination of host cell factors required for S. flexneri pathogenesis in vivo has proven difficult due to limited host susceptibility. Here we report the development of a pathogenesis system that involves the use of Caenorhabditis elegans as a model organism to study S. flexneri virulence determinants and host molecules required for pathogenesis. We show that S. flexneri-mediated killing of C. elegans correlates with bacterial accumulation in the intestinal tract of the animal. The S. flexneri virulence plasmid, which encodes a type III secretory system as well as various virulence determinants crucial for pathogenesis in mammalian systems, was found to be required for maximal C. elegans killing. Additionally, we demonstrate that ABL-1, the C. elegans homolog of the mammalian c-Abl nonreceptor tyrosine kinase ABL1, is required for S. flexneri pathogenesis in nematodes. These data demonstrate the feasibility of using C. elegans to study S. flexneri pathogenesis in vivo and provide insight into host factors

that contribute to S. flexneri pathogenesis. Copyright .COPYRGT. 2006, American Society for Microbiology. All Rights Reserved.

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ACCESSION NUMBER: 2005456852 EMBASE Full-text
TITLE: Abl kinases regulate actin comet tail elongation via an N-WASP-dependent pathway.
AUTHOR: **Burton E.A.**; Oliver T.N.; **Pendergast A.M.**
CORPORATE SOURCE: A.M. Pendergast, Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, United States. pende014@mc.duke.edu
SOURCE: Molecular and Cellular Biology, (2005) Vol. 25, No. 20, pp. 8834-8843. .
Refs: 54
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Oct 2005
Last Updated on STN: 27 Oct 2005

AB Microbial pathogens have evolved diverse strategies to modulate the host cell cytoskeleton to achieve a productive infection and have proven instrumental for unraveling the molecular machinery that regulates actin polymerization. Here we uncover a mechanism for Shigella flexneri-induced actin comet tail elongation that links Abl family kinases to N-WASP-dependent actin polymerization. We show that the Abl kinases are required for Shigella actin comet tail formation, maximal intracellular motility, and cell-to-cell spread. Abl phosphorylates N-WASP, a host cell protein required for actin comet tail formation, and mutation of the Abl phosphorylation sites on N-WASP impairs comet tail elongation. Furthermore, we show that defective comet tail formation in cells lacking Abl kinases is rescued by activated forms of N-WASP. These data demonstrate for the first time that the Abl kinases play a role in the intracellular motility and intercellular dissemination of Shigella and uncover a new role for Abl kinases in the regulation of pathogen motility. Copyright .COPYRGT. 2005, American Society for Microbiology. All Rights Reserved.

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ACCESSION NUMBER: 2003463973 EMBASE Full-text
TITLE: Erratum: Abl tyrosine kinases are required for infection by Shigella flexneri (EMBO Journal (2003) 22 (5471-5479)).
AUTHOR: **Burton E.A.**; Plattner R.; **Pendergast A.M.**
SOURCE: EMBO Journal, (3 Nov 2003) Vol. 22, No. 21, pp. 5962. .
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 2003
Last Updated on STN: 29 Dec 2003

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ACCESSION NUMBER: 2003420933 EMBASE Full-text

TITLE: Abl tyrosine kinases are required for infection by Shigella flexneri.
AUTHOR: **Burton E.A.**; Plattner R.; **Pendergast A.M.**
CORPORATE SOURCE: A.M. Pendergast, Duke University Medical Center, Dept. of Pharmacol. and Cancer Biol., Durham, NC 27710, United States. pende014@mc.duke.edu
SOURCE: EMBO Journal, (15 Oct 2003) Vol. 22, No. 20, pp. 5471-5479.
Refs: 41
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Nov 2003
Last Updated on STN: 6 Nov 2003

AB Infection by the opportunistic bacterial pathogen Shigella flexneri stimulates tyrosine phosphorylation of host cell proteins, but the kinases involved and their effects on the regulation of cell signaling pathways during bacterial entry remain largely undefined. Here, we demonstrate a requirement for the Abl family of tyrosine kinases during Shigella internalization. Family members Abl and Arg are catalytically activated upon Shigella infection, accumulate at the site of bacterial entry, and are required for efficient bacterial uptake, as internalization is blocked upon targeted deletion of these kinases or treatment with a specific pharmacological inhibitor. We identify the adapter protein Crk as a target for Abl kinases during Shigella uptake, and show that a phosphorylation-deficient Crk mutant significantly inhibits bacterial uptake. Moreover, we define a novel signaling pathway activated during Shigella entry that links Abl kinase phosphorylation of Crk to activation of the Rho family GTPases Rac and Cdc42. Together, these findings reveal a new role for the Abl kinases, and suggest a novel approach to treatment of Shigella infections through inhibition of host cell signaling pathways.

L65 ANSWER 22 OF 35 EMBASE
ACCESSION NUMBER: 2003157004 EMBASE Full-text
TITLE: A new link between the c-Abl tyrosine kinase and phosphoinositide signalling through PLC-γ1.
AUTHOR: Plattner R.; Irvin B.J.; Guo S.; Blackburn K.; Kazlauskas A.; Abraham R.T.; York J.D.; **Pendergast A.M.**
CORPORATE SOURCE: A.M. Pendergast, Proteomic Technologies, GlaxoSmithKline Research, Triangle Park, NC 27709, United States. pende014@mc.duke.edu
SOURCE: Nature Cell Biology, (1 Apr 2003) Vol. 5, No. 4, pp. 309-319.
Refs: 46
ISSN: 1465-7392 CODEN: NCBIFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2003
Last Updated on STN: 1 May 2003

AB The c-Abl tyrosine (Tyr) kinase is activated after platelet-derived-growth factor receptor (PDGFR) stimulation in a manner that is partially dependent on Src kinase activity. However, the activity of Src kinases alone is not sufficient for activation of c-Abl by PDGFR. Here we show that functional phospholipase C-γ1 (PLC-γ1) is required for c-Abl activation by PDGFR. Decreasing cellular levels of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P(2)) by PLC-γ1-mediated hydrolysis or dephosphorylation by an inositol polyphosphate 5-phosphatase (Inp54) results in increased Abl kinase activity. c-Abl functions downstream of PLC-γ1, as expression of **kinase-inactive c-Abl blocks**
PLC-γ1-induced chemotaxis towards PDGF-BB. PLC-γ1 and c-Abl form a complex in cells that is enhanced by PDGF stimulation. After activation, c-Abl phosphorylates PLC-γ1 and negatively modulates its function in vivo. These findings uncover a newly discovered functional interdependence between non-receptor Tyr kinase and lipid signalling pathways.

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ACCESSION NUMBER: 1998134399 EMBASE Full-text
TITLE: Protein tyrosine phosphatase 1B **antagonizes** signalling by oncoprotein tyrosine **kinase** p210 bcr-**abl** in vivo.
AUTHOR: Lamontagne K.R. Jr.; Flint A.J.; Franza B.R. Jr.; **Pendergast A.M.**; Tonks N.K.
CORPORATE SOURCE: N.K. Tonks, Cold Spring Harbor Laboratory, Demerec Building, 1 Bungtown Road, Cold Spring Harbor, NY 11724-2208, United States. tonks@cshl.org
SOURCE: Molecular and Cellular Biology, (1998) Vol. 18, No. 5, pp. 2965-2975. .
Refs: 64
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998

AB The p210 bcr-abl protein tyrosine kinase (PTK) appears to be directly responsible for the initial manifestations of chronic myelogenous leukemia (CML). In contrast to the extensive characterization of the PTK and its effects on cell function, relatively little is known about the nature of the protein tyrosine phosphatases (PTPs) that may modulate p210 bcr-abl-induced signalling. In this study, we have demonstrated that expression of PTP1B is enhanced specifically in various cells expressing p210 bcr-abl, including a cell line derived from a patient with CML. This effect on expression of PTP1B required the kinase activity of p210 bcr-abl and occurred rapidly, concomitant with maximal activation of a temperature-sensitive mutant of the PTK. The effect is apparently specific for PTP1B since, among several PTPs tested, we detected no change in the levels of TCPTP, the closest relative of PTP1B. We have developed a strategy for identification of physiological substrates of individual PTPs which utilizes substrate-trapping mutant forms of the enzymes that retain the ability to bind to substrate but fail to catalyze efficient dephosphorylation. We have observed association between a substrate-trapping mutant of PTP1B (PTP1B-D181A) and p210 bcr-abl, but not v- Abl, in a cellular context. Consistent with the trapping data, we observed dephosphorylation of p210 bcr-abl, but not v-Abl, by PTP1B in vivo. We have demonstrated that PTP1B inhibited binding of the adapter protein Grb2 to p210 bcr-abl and

suppressed p210 bcr-abl-induced transcriptional activation that is dependent on Ras. These results illustrate selectivity in the effects of PTPs in a cellular context and suggest that PTP1B may function as a specific, negative regulator of p210 bcr-abl signalling in vivo.

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ACCESSION NUMBER: 97032170 EMBASE Full-text
DOCUMENT NUMBER: 1997032170
TITLE: The BCR-ABL tyrosine kinase inhibits apoptosis by activating a Ras-dependent signaling pathway.
AUTHOR: Cortez D.; Stoica G.; Pierce J.H.; **Pendergast A.M.**
CORPORATE SOURCE: A.M. Pendergast, Department of Pharmacology, Duke University Medical Center, Durham, NC 27710, United States
SOURCE: Oncogene, (1996) Vol. 13, No. 12, pp. 2589-2594. .
Refs: 25
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 1997
Last Updated on STN: 18 Feb 1997

AB BCR-ABL is a deregulated tyrosine kinase that is expressed in Philadelphia chromosome (Ph1) positive human leukemias. When expressed in hematopoietic cells, BCR-ABL causes cytokine independent proliferation, induces tumorigenic growth and prevents apoptosis in response to cytokine deprivation or DNA damage. One mechanism by which BCR-ABL signals in cells is by activating the small guanine nucleotide binding protein Ras. BCR-ABL-transformed cells have constitutively high levels of active, GTP-bound Ras. Here we use 32D cells that inducibly express a dominant negative Ras protein to define the Ras requirements in BCR-ABL-transformed cells. Dominant negative Ras inhibits BCR-ABL-mediated Ras activation, and induces cell death by an apoptotic mechanism. Therefore, BCR-ABL inhibits apoptosis through activation of a Ras-dependent signaling pathway.

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ACCESSION NUMBER: 91303481 EMBASE Full-text
DOCUMENT NUMBER: 1991303481
TITLE: Evidence for regulation of the human ABL tyrosine kinase by a cellular inhibitor.
AUTHOR: **Pendergast A.M.**; Muller A.J.; Havlik M.H.; Clark R.; McCormick F.; Witte O.N.
CORPORATE SOURCE: Department of Microbiology, Mol. Genet./Mol. Biology Inst., University of California,Los Angeles, CA 90024, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1991) Vol. 88, No. 13, pp. 5927-5931. .
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Dec 1991
Last Updated on STN: 18 Dec 1991

AB Phosphotyrosine cannot be detected on normal human ABL protein-tyrosine kinases, but activated oncogenic forms of the human ABL protein are phosphorylated on tyrosine in vivo. Activation of ABL can occur by substitution of the ABL first exon with breakpoint cluster region (BCR) sequences or by deletion of the noncatalytic SH3 (src homology region 3) domain. An alternative mode for the activation of the ABL kinases is hyperexpression at >500-fold over endogenous levels. This is not a consequence of transphosphorylation of the hyperexpressed ABL molecules. ABL proteins translated in vitro lack phosphotyrosine, but tyrosine kinase activity is uncovered after immunoprecipitation and removal of lysate components. The rates of dephosphorylation of ABL and BCR-ABL fusion protein by phosphotyrosine-specific phosphatases are approximately the same. These combined results indicate that inhibition of ABL activity is reversible and suggest that a cellular component interacts noncovalently with ABL to inhibit its autophosphorylation.

L65 ANSWER 26 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:420923 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600410134
TITLE: The Caenorhabditis elegans ABL-1 tyrosine kinase is required for Shigella flexneti pathogenesis.
AUTHOR(S): **Burton, Elizabeth A.; Pendergast, Ann Marie** [Reprint Author]; Aballay, Alejandro
CORPORATE SOURCE: Duke Univ, Med Ctr, Dept Pharmacol and Canc Biol, Durham, NC 27710 USA
pende014@mc.duke.edu; a.aballay@duke.edu
SOURCE: Applied and Environmental Microbiology, (JUL 2006) Vol. 72, No. 7, pp. 5043-5051.
CODEN: AEMIDF. ISSN: 0099-2240.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 2006
Last Updated on STN: 23 Aug 2006

AB Shigellosis is a diarrheal disease caused by the gram-negative bacterium Shigella flexneri. Following ingestion of the bacterium, S. flexneri interferes with innate immunity, establishes an infection within the human colon, and initiates an inflammatory response that results in destruction of the tissue lining the gut. Examination of host cell factors required for S. flexneri pathogenesis in vivo has proven difficult due to limited host susceptibility. Here we report the development of a pathogenesis system that involves the use of Caenorhabditis elegans as a model organism to study S. flexneri virulence determinants and host molecules required for pathogenesis. We show that S. flexneri-mediated killing of C. elegans correlates with bacterial accumulation in the intestinal tract of the animal. The S. flexneri virulence plasmid, which encodes a type III secretory system as well as various virulence determinants crucial for pathogenesis in mammalian systems, was found to be required for maximal C. elegans killing. Additionally, we demonstrate that ABL-1, the C. elegans homolog of the mammalian c-Abl nonreceptor tyrosine kinase ABL1, is required for S. flexneri pathogenesis in nematodes. These data demonstrate the feasibility of using C. elegans to study S. flexneri pathogenesis in vivo and provide insight into host factors that contribute to S. flexneri pathogenesis.

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STN

ACCESSION NUMBER: 2006:22276 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600025141
TITLE: Abl kinases regulate actin comet tail elongation via an N-WASP-dependent pathway.
AUTHOR(S): **Burton, Elizabeth A.**; Oliver, Timothy N.; **Pendergast, Ann Marie** [Reprint Author]
CORPORATE SOURCE: Duke Univ, Med Ctr, Dept Pharmacol and Canc Biol, Durham, NC 27710 USA
pende014@mc.duke.edu
SOURCE: Molecular and Cellular Biology, (OCT 2005) Vol. 25, No. 20, pp. 8834-8843.
CODEN: MCEBD4. ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 2005
Last Updated on STN: 21 Dec 2005

AB Microbial pathogens have evolved diverse strategies to modulate the host cell cytoskeleton to achieve a productive infection and have proven instrumental for unraveling the molecular machinery that regulates actin polymerization. Here we uncover a mechanism for Shigella flexneri-induced actin comet tail elongation that links Abl family kinases to N-WASP-dependent actin polymerization. We show that the Abl kinases are required for Shigella actin comet tail formation, maximal intracellular motility, and cell-to-cell spread. Abl phosphorylates N-WASP, a host cell protein required for actin comet tail formation, and mutation of the Abl phosphorylation sites on N-WASP impairs comet tail elongation. Furthermore, we show that defective comet tail formation in cells lacking Abl kinases is rescued by activated forms of N-WASP. These data demonstrate for the first time that the Abl kinases play a role in the intracellular motility and intercellular dissemination of Shigella and uncover a new role for Abl kinases in the regulation of pathogen motility.

L65 ANSWER 28 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:578495 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300584128
TITLE: Abl tyrosine kinases are required for infection by Shigella flexneri.
AUTHOR(S): **Burton, Elizabeth A.**; Plattner, Rina; **Pendergast, Ann Marie** [Reprint Author]
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
pende014@mc.duke.edu
SOURCE: EMBO (European Molecular Biology Organization) Journal, (October 15 2003) Vol. 22, No. 20, pp. 5471-5479. print.
ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB Infection by the opportunistic bacterial pathogen Shigella flexneri stimulates tyrosine phosphorylation of host cell proteins, but the kinases involved and their effects on the regulation of cell signaling pathways during bacterial entry remain largely undefined. Here, we demonstrate a requirement for the Abl family of tyrosine kinases during Shigella internalization. Family members Abl and Arg are catalytically activated upon Shigella infection, accumulate at the site of bacterial entry, and are required for efficient bacterial uptake, as internalization is blocked upon targeted deletion of these kinases or treatment with a specific pharmacological inhibitor. We

identify the adapter protein Crk as a target for Abl kinases during Shigella uptake, and show that a phosphorylation-deficient Crk mutant significantly inhibits bacterial uptake. Moreover, we define a novel signaling pathway activated during Shigella entry that links Abl kinase phosphorylation of Crk to activation of the Rho family GTPases Rac and Cdc42. Together, these findings reveal a new role for the Abl kinases, and suggest a novel approach to treatment of Shigella infections through inhibition of host cell signaling pathways.

L65 ANSWER 29 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:306654 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300306654
TITLE: A new link between the c-Abl tyrosine kinase and phosphoinositide signalling through PLC-gamma1.
AUTHOR(S): Plattner, Rina; Irvin, Brenda J.; Guo, Shuling; Blackburn, Kevin; Kazlauskas, Andrius; Abraham, Robert T.; York, John D.; **Pendergast, Ann Marie** [Reprint Author]
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA pende014@mc.duke.edu
SOURCE: Nature Cell Biology, (April 2003) Vol. 5, No. 4, pp. 309-319. print.
ISSN: 1465-7392 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 22 Aug 2003

AB The c-Abl tyrosine (Tyr) kinase is activated after platelet-derived-growth factor receptor (PDGFR) stimulation in a manner that is partially dependent on Src kinase activity. However, the activity of Src kinases alone is not sufficient for activation of c-Abl by PDGFR. Here we show that functional phospholipase C-gamma1 (PLC-gamma1) is required for c-Abl activation by PDGFR. Decreasing cellular levels of phosphatidylinositol- 4,5-bisphosphate (PtdIns(4,5)P2) by PLC-gamma1-mediated hydrolysis or dephosphorylation by an inositol polyphosphate 5-phosphatase (Inp54) results in increased Abl kinase activity. c-Abl functions downstream of PLC-gamma1, as expression of **kinase-inactive c-Abl blocks** PLC-gamma1-induced chemotaxis towards PDGF-BB. PLC-gamma1 and c-Abl form a complex in cells that is enhanced by PDGF stimulation. After activation, c-Abl phosphorylates PLC-gamma1 and negatively modulates its function in vivo. These findings uncover a newly discovered functional interdependence between non-receptor Tyr kinase and lipid signalling pathways.

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ACCESSION NUMBER: 2003:283184 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300283184
TITLE: ROLE FOR ABL KINASES IN POSTSYNAPTIC ASSEMBLY AT THE NEUROMUSCULAR JUNCTION.
AUTHOR(S): Finn, A. J. [Reprint Author]; **Pendergast, A. M.** [Reprint Author]; Feng, G.
CORPORATE SOURCE: Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 234.3. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002.

Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jun 2003
Last Updated on STN: 19 Jun 2003

AB Agrin signaling through the receptor tyrosine kinase MuSK leads to profound clustering of acetylcholine receptors (AChRs) on the postsynaptic membrane of the neuromuscular junction (NMJ). This stands as the paradigm for first messenger-induced synaptogenesis in the nervous system. Nonetheless, the signaling network downstream of agrin/MuSK remains largely uncharacterized, despite a long known requirement for nonreceptor tyrosine kinase activity. Abl and the Abl-related gene (ARG) define a family of nonreceptor tyrosine kinases implicated in both cell adhesion and neural development. We hypothesized a novel postsynaptic role for this family in synaptogenesis and here show evidence of such at the NMJ. Specifically, the Arg tyrosine kinase is expressed in mouse muscle and localizes to the NMJ. This localization has a temporal pattern consistent with a role in synaptogenesis. In addition, denervation studies demonstrate that a significant pool of Arg at the NMJ is postsynaptic. Most strikingly, we show that either STI-571, a specific **inhibitor** of **Abl kinase** activity, or a dominant-interfering Abl allele blocks agrin-induced AChR clustering in cultured myotubes. We conclude that Abl kinases transduce signals in the agrin/MuSK pathway to effect assembly of the postsynaptic apparatus.

L65 ANSWER 31 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:186443 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300186443
TITLE: Identification of a novel signaling pathway required for uptake of bacterial pathogens.
AUTHOR(S): **Burton, E. A.** [Reprint Author]; **Pendergast, A.** [Reprint Author]
CORPORATE SOURCE: Pharmacology and Cancer Biology, Duke University, Durham, NC, USA
SOURCE: Molecular Biology of the Cell, (Nov 2002) Vol. 13, No. Supplement, pp. 51a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology. San Francisco, CA, USA. December 14-18, 2002. American Society for Cell Biology.
ISSN: 1059-1524 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Apr 2003
Last Updated on STN: 16 Apr 2003

L65 ANSWER 32 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:255344 BIOSIS Full-text
DOCUMENT NUMBER: PREV199800255344
TITLE: Protein tyrosine phosphatase 1B **antagonizes** signalling by oncoprotein tyrosine **kinase** p210 **bcr-abl** in vivo.
AUTHOR(S): Lamontagne, Kenneth R., Jr.; Flint, Andrew J.; Franza, B. Robert, Jr.; **Pendergast, Ann Marie**; Tonks, Nicholas K. [Reprint author]

CORPORATE SOURCE: Cold Spring Harbor Lab., Demerec Bldg., 1 Bungtown Rd., Cold Spring Harbor, NY 11724-2208, USA
SOURCE: Molecular and Cellular Biology, (May, 1998) Vol. 18, No. 5, pp. 2965-2975. print.
CODEN: MCEBD4. ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jun 1998
Last Updated on STN: 12 Aug 1998

AB The p210 bcr-abl protein tyrosine kinase (PTK) appears to be directly responsible for the initial manifestations of chronic myelogenous leukemia (CML). In contrast to the extensive characterization of the PTK and its effects on cell function, relatively little is known about the nature of the protein tyrosine phosphatases (PTPs) that may modulate p210 bcr-abl-induced signalling. In this study, we have demonstrated that expression of PTP1B is enhanced specifically in various cells expressing p210 bcr-abl, including a cell line derived from a patient with CML This effect on expression of PTP1B required the kinase activity of p210 bcr-abl and occurred rapidly, concomitant with maximal activation of a temperature-sensitive mutant of the PTK. The effect is apparently specific for PTP1B since, among several PTPs tested, we detected no change in the levels of TCPTP, the closest relative of PTP1B. We have developed a strategy for identification of physiological substrates of individual PTPs which utilizes substrate-trapping mutant forms of the enzymes that retain the ability to bind to substrate but fail to catalyze efficient dephosphorylation. We have observed association between a substrate-trapping mutant of PTP1B (PTP1B-D181A) and p210 bcr-abl, but not v-Abl, in a cellular context. Consistent with the trapping data, we observed dephosphorylation of p210 bcr-abl, but not v-Abl, by PTP1B in vivo. We have demonstrated that PTP1B inhibited binding of the adapter protein Grb2 to p210 bcr-abl and suppressed p210 bcr-abl-induced transcriptional activation that is dependent on Ras. These results illustrate selectivity in the effects of PTPs in a cellular context and suggest that PTP1B may function as a specific, negative regulator of p210 bcr-abl signalling in vivo.

L65 ANSWER 33 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:86239 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799377952
TITLE: The BCR-ABL tyrosine kinase inhibits apoptosis by activating a Ras-dependent signaling pathway.
AUTHOR(S): Cortez, David; Stoica, Gerald; Pierce, Jacalyn H.; Pendergast, Ann Marie [Reprint author]
CORPORATE SOURCE: Dep. Pharmacol., Duke Univ. Med. Cent., Durham, NC 27710, USA
SOURCE: Oncogene, (1996) Vol. 13, No. 12, pp. 2589-2594.
CODEN: ONCNES. ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1997
Last Updated on STN: 2 Apr 1997

AB BCR-ABL is a deregulated tyrosine kinase that is expressed in Philadelphia chromosome (Ph-1) positive human leukemias. When expressed in hematopoietic cells, BCR-ABL causes cytokine independent proliferation, induces tumorigenic growth and prevents apoptosis in response to cytokine deprivation or DNA damage. One mechanism by which BCR-ABL signals in cells is by activating the small guanine nucleotide binding protein Ras. BCR-ABL-transformed cells have constitutively high levels of active, GTP-bound Ras. Here we use 32D cells that inducibly express a dominant negative Ras protein to define the Ras

requirements in BCR-ABL-transformed cells. Dominant negative Ras inhibits BCR-ABL-mediated Ras activation, and induces cell death by an apoptotic mechanism. Therefore, BCRABL inhibits apoptosis through activation of a Rasdependent signaling pathway.

L65 ANSWER 34 OF 35 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:388818 BIOSIS Full-text
DOCUMENT NUMBER: PREV199192066133; BA92:66133
TITLE: EVIDENCE FOR REGULATION OF THE HUMAN **ABL** TYROSINE **KINASE** BY A CELLULAR **INHIBITOR.**
AUTHOR(S): **PENDERGAST A M** [Reprint author]; MULLER A J; HAVLIK M H; CLARK R; MCCORMICK F; WITTE O N
CORPORATE SOURCE: DEP MICROBIOL MOL GENETICS MOL BIOL INST, UNIV CALIFORNIA, LOS ANGELES, CALIF 90024, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1991) Vol. 88, No. 13, pp. 5927-5931.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Aug 1991
Last Updated on STN: 27 Aug 1991

AB Phosphotyrosine cannot be detected on normal human ABL protein-tyrosine kinases, but activated oncogenic forms of the human ABL protein are phosphorylated on tyrosine in vivo. Activation of ABL can occur by substitution of the ABL first exon with breakpoint cluster region (BCR) sequences or by deletion of the noncatalytic SH3 (src homology region 3) domain. An alternative mode for the activation of the ABL kinases is hyperexpression at > 500-fold over endogenous levels. This is not a consequence of transphosphorylation of the hyperexpressed ABL molecules. ABL proteins translated in vitro lack phosphotyrosine, but tyrosine kinase activity is uncovered after immunoprecipitation and removal of lysate components. The rates of dephosphorylation of ABL and BCR-ABL fusion protein by phosphotyrosine-specific phosphatases are approximately the same. These combined results indicate that inhibition of ABL activity is reversible and suggest that a cellular component interacts noncovalently with ABL to inhibit its autophosphorylation.

L65 ANSWER 35 OF 35 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-120256 [13] WPIX
DOC. NO. CPI: C2005-040028
TITLE: Screening test compounds involves assaying the test compounds for **inhibiting Abl kinase** activity and candidate agent for use in preventing or treating pathogen infection.
DERWENT CLASS: B04 D16
INVENTOR(S): **BURTON, E A; PENDERGAST, A M**
PATENT ASSIGNEE(S): (UYDU-N) UNIV DUKE
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2005003377	A1	20050106	(200513)*		20

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005003377	A1 Provisional	US 2002-432989P	20021213
	Provisional	US 2003-507088P	20031001
		US 2003-734582	20031215

PRIORITY APPLN. INFO: US 2003-734582 20031215; US 2002-432989P 20021213; US 2003-507088P 20031001

AB US2005003377 A UPAB: 20050224

NOVELTY - Screening test compounds comprising assaying the test compounds for the ability to **inhibit Abl kinase** activity, is new. The test compound that **inhibits Abl kinase** activity is a candidate agent for use in preventing or treating a pathogen infection.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of preventing or treating a pathogen infection comprising administering to a mammal, e.g. human an **inhibitor** of **Abl** tyrosine **kinase** to effect the prevention or treatment.

ACTIVITY - Antibacterial; Virucide.

MECHANISM OF ACTION - **Abl** tyrosine **kinase inhibitor.**

No biological data given.

USE - The method is useful for screening test compounds useful for preventing or treating pathogen infection in mammal, e.g. human (claimed), cats, dogs, cattle, pigs, or horses.

ADVANTAGE - The resulting compound is capable of blocking pathogen infection in mammal. It results in decrease in sub-state phosphorylation thus it is capable in preventing and treating pathogen infection. Dwg.0/9

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